Evidence Review Group Report commissioned by the NHS R&D Programme on behalf of NICE

Imatinib as adjuvant treatment following resection of KIT-positive gastrointestinal stromal tumours

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Abbreviations

AE	Adverse event
AT	Adjuvant treatment
BSC	Best supportive care
CEAC	Cost effectiveness acceptability curve
CSR	Clinical study report
ERG	Evidence review group
GIST	Gastrointestinal stromal tumour
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat analysis
LY	Life year
MP	Monthly probability
OS	Overall survival
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
QoL	Quality of life
RFS	Recurrence free survival
RCT	Randomised controlled trial
SA	Sensitivity analysis
SPC	Summary of product characteristics

Commercial in Confidence (CIC) data is highlighted in blue

1 SUMMARY

1.1 Scope of the submission

The scope was to assess the clinical and cost-effectiveness of imatinib as adjuvant treatment for adult patients who are at significant risk of relapse following resection of KIT positive gastrointestinal stromal tumours.

1.2 Summary of submitted clinical effectiveness evidence

Clinical evidence was derived mainly from one randomised double-blind clinical trial (the Z9001 trial) comparing one year of adjuvant imatinib with placebo. On disease progression, all patients received treatment with imatinib or other treatment options as appropriate regardless of treatment arm they were allocated to. Patients in the 'significant risk' sub-group of the trial are likely to be similar to an eligible UK population. Patients who had already received imatinib for advanced GIST and then became eligible for resection were excluded, however, this is likely to be a small group and not comparable to those receiving imatinib for the first time after resection.

There was a clear delay in recurrence in the adjuvant imatinib arm, with a difference in median time to recurrence of 20.7 months, HR of 0.257 (0.150-0.442), p<0.001). There was little difference in overall survival with median time to survival not reached in either treatment arm.

1.3 Summary of submitted cost effectiveness evidence

The manufacturers submitted estimates of the incremental cost effectiveness of imatinib therapy compared to surgical resection alone. In the base case, the population was defined as those at moderate or severe risk of recurrence (in line with the scope of the appraisal) following surgery who receive three years of imatinib. The manufacturer's estimate of the base case ICER was £22,937/QALY. This was revised in the response to clarifications to £23,601 after an error was discovered in the model by the manufacturer. The manufacturer's base case analysis suggests that there is approximately a

60% chance that imatinib is cost-effective at willingness to pay thresholds of between £20,000 to £30,000 per QALY. Four additional analyses were submitted: (a) Significant risk patients, receiving imatinib for one year; (b) The overall at-risk population (no treatment time specified); (c) The high-risk only population, receiving one year of imatinib and (d) The high-risk only population, receiving three years of imatinib; with ICERS of £13,550, £32,981, £6,109 and £19,813 respectively.

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

Although based on a single trial, and associated with some uncertainties, there is clear evidence for a delay in disease recurrence in the short term.

The model structure used by the manufacturer reflects reasonably well the natural history of the disease and the ERG identified no programming errors in the model.

1.4.2 Weaknesses

The at significant risk sub-group of the Z9001, which is the relevant population for this appraisal, was based on a retrospective assessment of risk, did not include all patients, was not balanced at the start of the trial for important characteristics and may be subject to selection bias. However, these caveats do not overturn the clear delay in disease recurrence.

The data on which the results are based are immature. The planned follow-up for the trial is five years, however median follow-up times at time of analysis were much lower, at [redacted] for recurrence free survival and [redacted] for overall survival for the significant at risk group. The reason for this substantial difference between follow-up times was not explained.

The Z9001 trial measures the effect of adjuvant imatinib given for one year only, however the model base case assumes treatment for three years. Some data from uncontrolled studies with longer treatment duration are used to support assumptions made in the model, however treatment times in these studies also fall short of three years.

The model submitted by the manufacturer is complex and not readily amenable to changes in input values. The complexity of the model and the lack of obvious user interface for most parameters meant that the ERG was not confident that making a change to a value in a given cell of the Excel file would be appropriately reflected throughout the model calculations. This limited the scope for the ERG to fully validate the model and to undertake alternative analyses, and thus reduced the ERGs confidence in the results of the model.

1.4.3 Areas of uncertainty

A survival benefit with adjuvant imatinib has to date not been shown. There is a lack of good long-term evidence around the rate of imatinib resistance over time with different treatment strategies (+/- adjuvant imatinib, for one year or three years), and the effect on overall survival.

There is no evidence on the effect of adjuvant imatinib on recurrence free survival or overall survival in patients who have previously had imatinib for advanced disease and who then became eligible for resection; these patients were excluded from the Z9001 trial.

The ERG has concerns about a number of aspects of the submitted economic analysis:

- the modelling of the utility data in the analysis
- the lack of a utility decrement applied to patients experiencing adverse events from adjuvant imatinib
- the uncertainty around how monthly probabilities of death were derived and applied in the model
- the assumption of sustained benefit from treatment for two years beyond the evidence base
- the lack of clarity regarding how lifetime costs are used in the model
- the absence of probabilistic sensitivity analysis for the sub-groups provided

- the lack of sensitivity analysis around modelling recurrence free survival and the opaqueness of the submitted model

Whilst it is credible that the direction of effect of the majority of these problems is to inappropriately reduce the estimated Incremental Cost Effectiveness Ratio, the complexity and opaqueness of the submitted model made it effectively impossible for the ERG to undertake the desirable alternative analyses to quantify the impact. Therefore, the ERG can only advise that the submitted estimates be treated with considerable caution.

1.5 Key issues

- There is to date no evidence of an overall survival benefit (or disadvantage) with adjuvant imatinib, and no evidence that recurrence free survival is a good proxy for overall survival

- There is no good long-term data on potential differences in imatinib resistance (probability of recurrence) with treatment strategies including or excluding adjuvant imatinib

- Given this lack of data beyond one year, the ERG have concerns regarding the assumption in the economic model of sustained benefit from treatment for two years beyond the evidence base

- The submitted economic model was not readily amenable to changes in input parameters and there was limited scope for the ERG to validate or undertake alternative analyses, for example around recurrence free survival

- There are serious concerns around the validity and application in the model of a number of input parameters, such as utilities and monthly probabilities of death

- The model makes a basic assumption that any benefit in delay of recurrence translates directly into an increase in survival over the long term; this assumption is not supported by any evidence and does not take into account the possibility of differing rates of imatinib resistance between the two treatment arms

- Probabilistic sensitivity analysis was undertaken only for the base case, not for any other scenario analyses; no scenario analyses were undertaken on the choice of model used to estimate long-term survival data

- Due to the large number of uncertainties and assumptions, the estimated Incremental Cost Effectiveness Ratios should be regarded as highly uncertain

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The relevant patients to be considered for adjuvant imatinib are those who have had a resection of KIT (CD117) positive GIST and are deemed to be at significant risk of relapse. Patients who have a low or very low risk of recurrence are not to be considered for adjuvant imatinib. A definition of 'significant' risk is given below.

Epidemiology

The submission (p15) quotes a prevalence for GIST of 129 per million, and an annual incidence of between 6.8 and14.5 per million, based on the findings of studies in different countries. The submission assumes the upper end of the incidence rate range: 14.5 per million. A UK study[1] from 2008 identified by the ERG reported an incidence of 13.2 per million, which is in line with the figure quoted in the submission.

The submission does not give an estimate of survival times for patients in different risk groups. Disease stage, resection type and gender affect recurrence-free survival, whilst mutation types, presence of *KIT* or *PDGFRA* mutation, location of tumour and number of mitosis can predict overall survival.[2] The ERG found the following estimates: survival after resection ranged from 48% to 80% at 5 years before the introduction of imatinib; for low-risk GIST, the 5-year survival rate (approximately 95%) is similar to the normal population, whilst for high risk GISTs the 5-year survival rate ranged from 0% to 30% before the introduction of imatinib.[2] As imatinib is a relatively recent treatment for GIST, there are fewer long-term survival estimates. In the trial of imatinib for advanced GIST with the longest reported follow-up so far (Blanke 2008[3]) median survival increased from 18 months to 60 months.

Risk stratification

The submission provides details of the risk stratification criteria used for classification in the submission as shown below:

Taken from p17 of submission

Table 1: Risk stratification (Miettinen 2006)

Tumour Parameters		Risk of Developing Progressive Disease or Metastases During Long-term Follow-up (%)			
		Tumour Location			
Tumour Size	Mitotic Rate	Gastric	Jejunal/ileal	Duodenal	Rectal
≤ 2cm	≤ 5 per 50 HPFs	None (0)	None (0)	None (0)	None (0)
> 2 ≤ 5cm		Very Low (1.9)	Low (4.3)	Low(8.3)	Low (8.5)
>5 ≤ 10cm		Low (3.6)	**Moderate (24)**	**High (34)**	**High (57)[a]**
> 10cm		**Moderate (12)**	**High (52)**		
≤ 2cm	> 5 per 50 HPFs	None (0)[a]	**High (50)[a]**	-[b]	**High (54)**
> 2 ≤ 5cm		**Moderate (16)**	**High (73)**	**High (50)**	**High (52)**
>5 ≤ 10cm		**High (55)**	**High (85)**	**High (86)**	**High (71)**
> 10cm		**High (86)**	**High (90)**		

HPF = High powered field
a. denotes very small case numbers
b. insufficient data

'Significant ' risk includes both moderate and high-risk patients.

Different methods of risk stratification may be used and the NIH scheme (Fletcher 2002[4], see Appendix 3) is often favoured in the UK (expert opinion). It is uncertain how comparable patients are where they have been classified as having a similar risk using different indices. Following resection, 54.3% of patients are estimated to be at significant risk of relapse (see Appendix 1, data Table 7, p133). This estimate is based on the Z9001 trial, which included 773 patients. An estimate of risk was however only available for 556/773 patients and was based on retrospective assessment of risk factors using the Miettinen 2006[5] criteria. There is therefore some uncertainty associated with this estimate.

Resectability

The submission states that two thirds of GIST patients are thought to be resectable and appropriately references this statement. There is no background information on the use of imatinib in patients who are initially un-resectable and the proportion of these patients undergoing subsequent post-imatinib surgery. The number of these types of patients may be important to this submission because, in the licensed indication, these patients may be indicated for adjuvant GIST. However, these patients were excluded from the Z9001 trial and do not contribute to the data used in this submission. The importance of this omission is unclear since no data is provided on the relative numbers of patients taking this route of treatment.

KIT mutations

As stated in the submission, the majority of GIST patients are KIT positive and the licence only applies to this set of patients. However, even in KIT positive patients, primary resistance to imatinib may occur depending on the location of the *KIT* mutations. For example, for KIT positive patients with mutations in exon 11, good responses to imatinib have been observed, whereas, for those with mutations on exon 9, response is poorer and higher imatinib doses are required to achieve response.[6]

The immunohistochemical examination of tumour samples for diagnosis of GIST is described in the submission but no reference is made to the importance of specific types of *KIT* exon gene mutations. Since differences contribute substantially to predicting future response, it would have been useful to have a more complete description of the different possible immunohistochemical diagnoses and their likely effect on response to adjuvant treatment with imatinib.

Resistance to imatinib

The study by Demetri et al., (2002)[7] found that primary resistance occurred in 5% of patients, with another 14% developing early resistance. Another estimate of primary resistance to imatinib is 10-20%.[8]

The ERG notes that the issue of secondary resistance (resistance that develops whilst taking imatinib) is barely addressed in the manufacturer's submission (it is mentioned on p97 in the context of a sensitivity analysis). Most patients eventually show resistance to imatinib due to secondary mutations in the *KIT* and/or *PDGFRA* kinase domains. One study found that secondary or acquired resistance develops after a median of about two years of treatment.[9] It would have been useful to have a discussion of this issue in the background section of the submission since it is relevant to the subsequent economic model.

Sunitinib

There is no background information regarding the use of sunitinib, a tyrosine kinase receptor inhibitor. Since sunitinib is included as a further treatment option in the economic model, some discussion of its role in treatment and current use may have been appropriate.

The UK GIST guidelines[10] state that sunitinib should be considered in patients with unresectable and/or metastatic disease if they show disease progression on imatinib after dose escalation.

NICE guidance[11] from 2009 states that:

"Sunitinib is recommended, within its licensed indication, as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if:

• *imatinib treatment has failed because of resistance or intolerance, and*

• *the drug cost of sunitinib (excluding any related costs) for the first treatment cycle will be met by the manufacturer."*

The cost of imatinib (Gilvec®) is £1604.08 (400mg, 30-tab pack) and the cost of sunitinib (Sutent®) is £3138.80 (50mg, 28-cao pack).[12]

2.2 Critique of manufacturer's overview of current service provision

A treatment algorithm for GIST is provided in the submission, taken from the 'Guidelines for the management of gastrointestinal stromal tumours (GIST)'[10] from August 2009. Section 11.1.4 of these guidelines on adjuvant therapy suggests that there is preliminary evidence from the Z9001 trial that: "…*imatinib increases recurrence-free survival and may be an effective treatment to prevent recurrence following primary surgery*. T*he long term effects of adjuvant imatinib have yet to be thoroughly assessed, particularly in terms of the potential development of resistance on adjuvant imatinib, optimal imatinib dose, optimal duration of imatinib, and whether a significant overall survival benefit is gained*."

The guidelines further state that choice of patient (e.g. risk level, mutational status) is an issue that needs further clarification, and that the ongoing EORTC 62024 and SSGXVIII studies may provide information on survival benefit and optimal treatment duration (see 4.1.3 for further information on the ongoing trials).

Treatment recommendations regarding adjuvant imatinib are not specific in the guidelines, reflecting the uncertainty in this area:

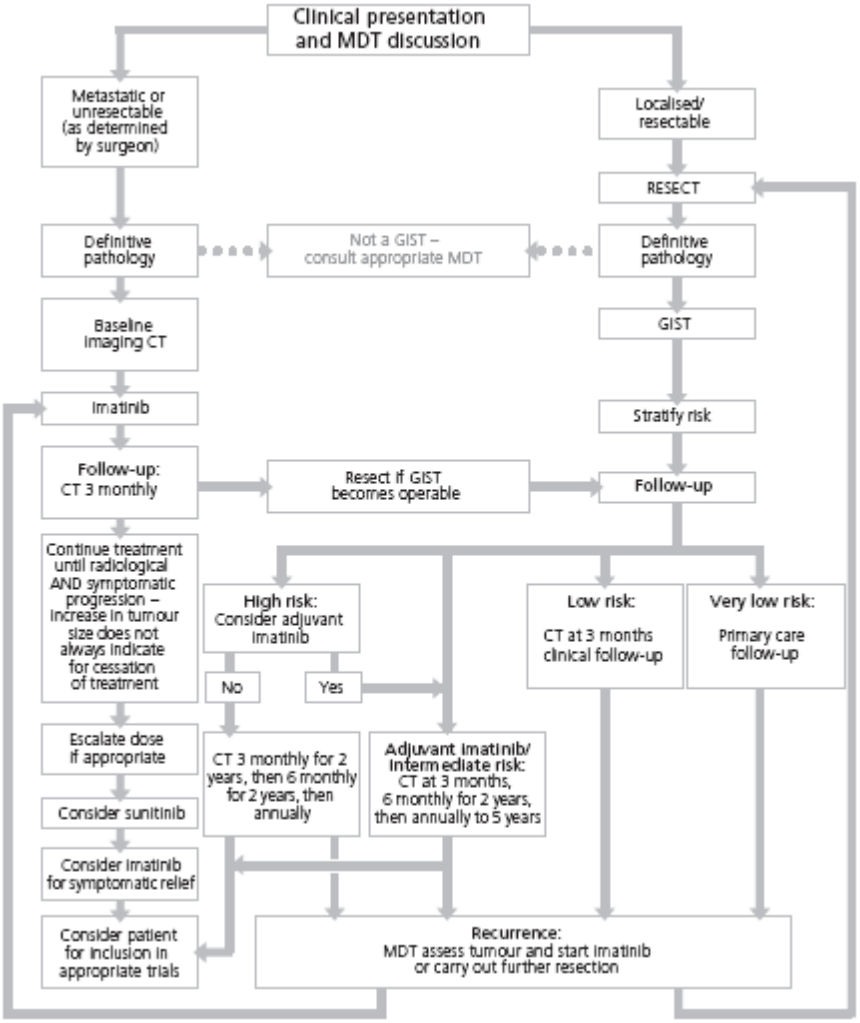
"Key recommendations-resectable disease[10]:

Patients should be considered for inclusion in clinical trials of neoadjuvant and adjuvant therapy.

Treatment following resection:

Adjuvant therapy with imatinib may be considered in patients predicted to have a high risk of recurrence."

Taken from submission (p21): Figure 2 Treatment algorithm for GIST



The submission does not give any details on current practice (i.e. is adjuvant imatinib already given, proportion of patients, type of patients etc.).

As stated in the submission, KIT testing (CD117 staining) is routinely conducted throughout the UK in the diagnosis of GIST (section 1.11). Mutational analysis is conducted in some centres (e.g. Birmingham) but is not standard practice. Tumour size and mitotic index are routinely assessed in the UK, and the NIH (Fletcher 2002)[4] scheme is widely used. The more complex Miettinen 2006[5] scheme is less widely used. It is possible that there would be

differences across the UK in how patients are classified as being at 'significant' risk.

3 Critique of manufacturer's definition of decision problem

3.1 Population

The population specified in the NICE scope is: adults who are at a significant risk of relapse following resection of KIT (CD117)-positive GIST. This is consistent with the decision problem in the submission. The bulk of the data in the submission is from patients in the Z9001 trial. These are all adult, KIT-positive patients. With regard to their being 'at significant risk', selection for the Z9001 trial was mainly by tumour size and did not include details on the mitotic index (which would be routinely assessed in the UK). Retrospective classification using the Miettinen 2006 risk stratification criteria found that very low and low risk patients were included. These patients should not be considered for adjuvant imatinib according to the UK licence. 556/713 (78%) patients randomised to the study had relevant data that allowed retrospective classification, and just over half (302/556) were assessed as being at significant risk (significant risk being comprised of moderate and high risk) and thus eligible:

Manufacturer's Table 8: (p45)

Table 2: Risk Stratification (Miettinen 2006) (N=556) for Z9001 trial patients

Very Low	115 (20.7%)
Low	139 (25.0%)
Moderate	137 (24.6%)
High	165 (29.7%)

These subgroups are based on 78% of randomised patients and there is thus a possibility of selection bias, though an additional report from the manufacturer supplied to the ERG (response document: Committee for Medicinal Products for Human Use (CHMP) assessment/questions) identified

no differences between the 78% of patients and the total population in terms of tumour size, tumour location, duration of treatment exposure or events. The relevant trial population (significant risk) is thus based on 302 patients. Baseline demographics were provided for this subgroup in response to a request from the ERG.

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

All included patients were KIT positive, with a tumour size of at least 3cm. All but one (status: unknown) of the patients had resection margins of RO (91.9%) or R1 (R0=microscopic clearance, R1=positive microscopic margins). There is no information from the trial on adherence to surgical standards.

It is likely that the significant at risk population from the trial is similar to a population in the UK that would be considered at significant risk. However, methods of classification may vary and there is the possibility of differing thresholds for considering a patient to be at significant risk. Clinical opinion suggests there is no difference in risk factors between different ethnic groups.

Not included in the Z9001 trial are patients who may have had previous imatinib for advanced disease, and who then reached a stage where resection was possible, and who then may be eligible for adjuvant imatinib. This is likely to be a small group and patients are unlikely to be comparable to those receiving imatinib for the first time after resection.

The patients in the included non-RCTs (15 studies) are in the main classified as 'high risk' and may therefore differ somewhat from the population classified as 'significant risk'. The Miettinen scheme was not used for categorising patients' risk in any of these studies.

The ERG notes that much of the relevant information on the 'significant risk' sub-group, which corresponds to the population in the license indication, was not provided in the initial submission. Further details were provided in response to clarification questions.

3.2 Intervention

The intervention is adjuvant imatinib (Glivec), a tyrosine kinase inhibitor. In the Z9001 trial it is given for one year.

Imatinib is licensed in the UK for: "The treatment of adult patients with KIT (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST) and the adjuvant treatment of adult patients who are at significant risk of relapse following resection of KIT (CD117)-positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment."[13] The Summary of Product Characteristics (SPC) further states that the optimal treatment duration with adjuvant imatinib is not yet established. Adjuvant imatinib was also approved by the FDA in 2008; there are no recommendations regarding which patients are most likely to benefit or guidance on the optimum duration.[14]

The UK 2009 guidelines (see section 2.2) state that patients should be considered for inclusion in clinical trials of neoadjuvant and adjuvant therapy and adjuvant therapy with imatinib may be considered in patients predicted to have a high risk of recurrence.

The ESMO 2009 guidelines[15] state there is as yet no global consensus in the medical community regarding adjuvant imatinib as standard treatment for GIST patients with localised disease. The guidelines do suggest that, based on currently available trial data, the use of adjuvant imatinib for one year may be supported in patients with a substantial risk of relapse (based on the Z9001 trial). It is further suggested that mutational analysis may guide the selection of those patients, who may be more likely to benefit from the treatment. Results of a trial comparing one versus three years adjuvant treatment are awaited (the SSG XVIII/AIO trial, see section 4.1.3, ongoing trials). Results are not expected before late 2010/11 and the ERG identified no interim results.

NICE guidance from 2004 is available for first-line treatment: "*Imatinib treatment at 400 mg/day is recommended as first-line management of people with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic gastro-intestinal stromal tumours (GISTs*)".[16]

3.3 Comparators

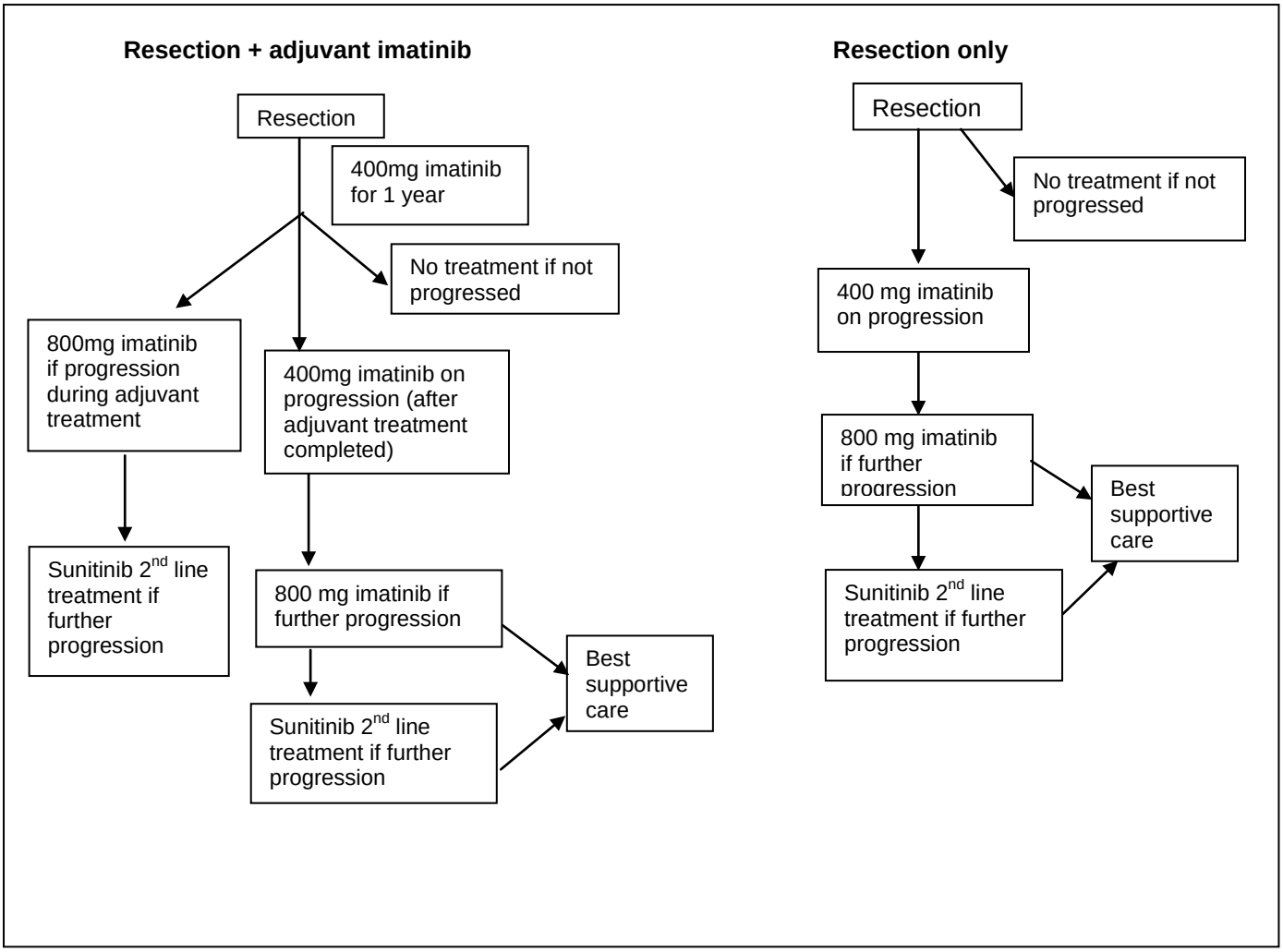
The relevant comparator as specified in the NICE scope is surgery (resection) without adjuvant imatinib therapy. This is also the comparator in the Z9001 trial. Resection only and adjuvant imatinib can be compared for the outcome of progression free survival, as patients are not scheduled to change their treatment unless they progress (though they may drop out due to side effects).

For overall survival, the treatment strategies being compared become more complex (see Figure 1). For the patients on the adjuvant arm, treatment options include: no further treatment (if no progression), dose escalation to imatinib 800mg if progression occurs during the 1-year treatment phase or re-treatment with imatinib (400mg) or sunitinib if progression occurs after the 1-year treatment period. For patients in the placebo arm, treatment options include: no treatment (if no progression), imatinib 400mg on progression and/or imatinib 800mg or sunitinib on further progression. There may also be

a small cohort of patients who, for various reasons, move directly to sunitinib or best supportive care (BSC). All patients are treated according to disease progression regardless of which treatment arm they are in. Figure 1 shows possible treatment pathways in the two treatment arms.

The economic model compares imatinib to resection surgery alone as specified in the scope. The base case considers three years treatment. One year treatment with adjuvant imatinib, as in the Z9001 trial, is considered in scenario analyses.

Figure 1 Treatment pathways



3.4 Outcomes

The manufacturer's decision problem lists the following outcomes, which are all appropriate: overall survival, recurrence-free survival (or progression free survival) and adverse events. Health-related quality of life has not been [redacted]

See section 4.1.6 for further comments.

3.5 Time frame

At the time of data analysis in the Z9001 trial, median follow-up time for recurrence and overall survival was 19.7 months in the DeMatteo publication[17]. In the submission, the median follow-up time is given as 14 months for recurrence free survival and 19.7 months for overall survival. It is not clear why there is this discrepancy. The ERG thinks it is possible that data on recurrence has not yet been collated/analysed, whilst the outcome of dead/alive is already known.

For the significant risk population, the median follow-up times were [redacted] for recurrence free survival, and [redacted] for overall survival. Again there is an unexplained discrepancy.

As can be seen from Figure 10 on p.48 of the submission, no difference in overall survival can be seen (total population) and in both treatment arms more than 90% of patients were still alive at 48 months. The numbers at risk at 48 months were 30 patients (total patient population) and [redacted] patients (significant risk population, details provided in clarification response).

The timeframe used in the economic model is lifetime. Modelled survival curves for both treatment arms are shown for a 20 year period (Figure19, p89). This period is likely to be appropriate given the relatively good survival of patients with imatinib, but there is no Z9001 trial data on which to base the survival curves post 1-2 years.

Planned follow-up for the trial is five years. Accrual to the trial was stopped early (in April 2007), because the trial results crossed the interim analysis

efficacy boundary for recurrence free survival. It is unclear how long a trial would need to be to provide median overall survival estimates.

3.6 Other relevant factors

None identified.

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

4.1.1 Description of manufacturers search strategy and comment on whether the search strategy was appropriate.

Databases and other sources including unpublished sources, any restrictions.

Summary from the manufacturer's submission:

The following sources were searched between July and August 2009: Ovid MEDLINE In Process & Other Non-Indexed Citations & Ovid MEDLINE 1950 – search date; EMBASE (Ovid) 1980 – search date; Science Citation Index (via Web of Knowledge) [no date span of search provided]; Cochrane Library [date and issue number not given] including Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register and Database of Reviews of Effects. The current research registers www.Clinicaltrials.gov were also consulted via the WWW. Searches were supplemented by checking bibliographies of included studies, conference proceedings and consulting experts in the field. Date limits or language restrictions were not used on any database.

Comments:

- The search strategy for the Cochrane Library is not presented, neither is the year or issue number of the database indicated in the list of databases in section 6.1. Therefore the searches cannot be verified.

- The date span of the searches in Science Citation Index is not stated.
- Where the database search strategies are presented (all except Cochrane Library) they appear to be sound and would be unlikely to have missed relevant studies.

The searches which were done by the ERG of MEDLINE, EMBASE and Cochrane Library identified one additional trial which may potentially have been relevant to this submission (see 4.1.4)

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

The inclusion and exclusion criteria were in the main clearly defined (on p25 of submission). Patients eligible for inclusion were those at significant risk of recurrence. There was no definition of significant risk, and it appears that all studies were included regardless of how the authors defined risk. All study designs were included; depending on the design some of these may not contribute much valuable information, particularly where there was no control group or where 'significant risk' was poorly defined or different to that of an eligible UK population. Foreign language papers were excluded.

4.1.3 Table of identified studies. What studies were included in the submission and what were excluded?

There is one included RCT, the Z9001 study. This study has been published and is available in the public domain (DeMatteo 2009[17]). The submission states on p35 (3rd paragraph) that some data are reported differently in the DeMatteo publication and the Clinical Study Report (CSR). Much of the CSR data has been highlighted as CIC in the company submission.

A further 15 non-randomised studies were included: three uncontrolled phase II studies (n= 47, n=57 and n=107), three cohort studies (n=5, n=23 and n=56) and nine case reports. Patients are all described as high risk (one population as intermediate/high risk).

Four ongoing trials were identified in the submission. The EORTEC 62024 trial is a 5-year randomised controlled trial comparing 400mg adjuvant imatinib daily for two years to no additional therapy in 750 (planned) adults who are at intermediate or high risk of recurrence after resection. The primary outcome was overall survival, however our clinical expert has advised us that this has recently been changed to disease free survival. The SSG XVIII/A1 trial is also a randomised trial in 280 (planned) high/very high risk patients comparing 400mg adjuvant imatinib daily over 12 months compared to 36 months, the primary outcome is recurrence free survival. It is possible that these two trials will provide additional information on overall survival and optimal treatment length. The patient populations are also more relevant as they do not include low risk patients. The submission states that interim analyses are expected 2010/11, and the ERG has not been able to identify any data in the public domain.

Two further single arm studies were detailed in the submission. In the NCT00867113 trial an estimated 133 patients at intermediate to high risk will receive 400mg imatinib daily for five years. This study started in June 2009. The ERG has identified no preliminary data. In the NCT00171977 study an estimated 60 patients received 400mg imatinib daily for 48 weeks. This study started in June 2004. In response to clarification questions, an abstract[18] was provided for this study (see section 4.2.1, results of non-RCTs for a summary of results).

4.1.4 Details of any relevant studies that were not included in the submission ?

Details of the Nishida study[18] were provided on request (see above paragraph).

One study that included pre-operative as well as adjuvant imatinib was identified by the ERG (see description below).

The uncontrolled NCT00500188 study looked at pre and postoperative Imatinib in patients with c-KIT positive GIST. In this study, patients received imatinib for 7, 5 or 3 days before surgery and imatinib treatment was

continued for 2 years post surgery. Since imatinib was taken before surgical intervention, this study may not have been considered to fit the inclusion criteria for this submission. However, pre-surgical intervention was minimal and it appears unlikely that the health of patient population was very different to patient populations without pre-surgical imatinib. A publication of this trial[19] reported a median disease free survival (DFS) rate of 32 months (range 10-46 months) with DFS at 94% and 87% at 1 and 2 years respectively. Grade 3 or 4 adverse events were reported in 10 of 19 patients and four patients dropped out of the study due to toxicity from imatinib. Only 19 patients are reported in this publication and the information it provides may be limited compared to data from larger trials.

Ten papers were excluded by the manufacturer as they were not in English. The ERG requested further details which were provided: seven of the foreign language papers were case reports (1 or 2 patients), one included five patients and one up to 11 patients on adjuvant imatinib. One paper was an opinion/review. There were no RCTS, large cohorts or case series, and it is unlikely that any important information has been missed by excluding these papers.

4.1.5 Description and critique of manufacturers approach to validity assessment

The submission uses appropriate questions to assess the validity of the Z9001 trial (Table 7, p41 of submission). The manufacturer's responses and comments made by the ERG are listed below.

Criterion	Submission response	ERG comments
How was allocation concealed?	Central allocation	There is no further detail on allocation concealment, though central allocation suggests it may have been appropriate.
What randomisation technique was used?	Computer programme with a stratified biased coin design	This appears to be appropriate.
Was a justification of the sample size provided?	Yes	Yes, however this relates to the total study population including low risk patients. The 'at significant risk' group is a sub-group and comprises 302 patients. It is unclear whether the study was powered to find differences between study arms in this sub-group.
Was follow-up adequate?	Yes, although ongoing studies are assessing longer follow-up periods	The planned follow-up time is five years. At the time of data analysis, the median follow-up time for overall survival was 19.7 months [redacted], and for recurrence free survival was 14 months [redacted] Median recurrence free survival has not yet been reached for the overall patient group, [redacted] Median overall survival has not been reached in the total population group, [redacted]
Were the individuals undertaking the outcomes assessment aware of allocation?	No	The full publication states that patients and investigators were blinded to the group the patient was assigned to (up to the point of disease recurrence)
Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.	The design was parallel-group but patients assigned to placebo were eligible to crossover to imatinib treatment if tumour recurred. The primary endpoint was recurrence-free survival which was not affected by the option of crossing over from placebo to imatinib following tumour recurrence. However, the effect of imatinib on overall survival may be underestimated due to this.	The outcome of recurrence free survival will not be affected by patients crossing over from placebo to treatment, as treatment with imatinib will occur only on recurrence. Crossover to imatinib on progression will also not affect the outcome of overall survival as this is part of an overall treatment strategy (see 3.3)

Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	230 institutions in USA and Canada. Clinical practise is likely to be similar to UK practise for the intermediate and high risk patients. Low and very low risk patients should not receive adjuvant treatment as stated in the SmPC.	Agree, low/moderate risk patients would not be considered eligible to receive adjuvant imatinib in the UK. We don't know about adherence to surgical standards in the different countries.
How do the participants included in the RCT compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.	Patients were similar to those likely to receive the intervention in the UK (patients who had had resection of KIT-positive GIST measuring ≥3 cm). The retrospective analysis of the RCT permitted patients to be matched to the current risk stratification scheme as recommended in the UK GIST guidelines	It is likely that the significant risk population from the Z9001 trial (as classified retrospectively) is similar to a UK population that would be considered to be at significant risk. There is a possibility that risk thresholds may vary depending on classification system used. Not included in the Z9001 trial are patients who may have had previous advanced disease, became eligible for resection and who could then be considered eligible for adjuvant imatinib.
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	400mg imatinib daily, as recommended in the Summary of Product Characteristics.	If the patient experienced recurrence whilst on 400mg imatinib daily, the dose could be increased to 800 mg daily. There are no details in the SPC on dose escalation or post one year treatment.
Were the study groups comparable?	Yes	The study groups (total population) appear reasonably well balanced. For the significant risk sub-group, [redacted]
Were the statistical analyses used appropriate?	Yes	Statistical analyses appear appropriate.
Were there any withdrawals and/or discontinuation? Were these included in the analysis?	Patients discontinuing treatment early: - Imatinib: 97/359 (27%): 54 for adverse events, 1 for recurrence, 15 for patient withdrawal, 24 other/missing reasons. - Placebo: 87/354 (25%): 11 for adverse events, 41 for recurrence, 20 for patient withdrawal, 15 other/missing reasons. All were included in the analysis	Significant risk group: [redacted]

		[redacted]
Was an intention-to-treat analysis undertaken?	Yes	The ITT population was used for analyses. There are however no details in the submission on how missing data was handled, and what effect this might have on results. [redacted]
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	No	Crossovers are unlikely to affect interpretation of results as outlined above. We do not know how missing data might affect interpretation of results.

4.1.6 Description and critique of manufacturers outcome selection

Relevant outcome measures as specified in the NICE scope and the decision problem were overall survival (OS), recurrence-free survival (RFS), recurrence rates, adverse effects (AE)/toxicity and health related quality of life (HRQoL).

The manufacturer did not collect data on health-related quality of life during the trial using an appropriate preference based instrument such as the EQ-5D. Estimates of utility in the model were instead taken from published sources in the literature or were assumed by the manufacturer (see section 5.1.3).

The included RCT (Z9001) included all the above outcome measures except for HRQoL. It is unclear what the rationale was for not using any QoL instruments in this study. None of the non-RCTs used a QoL measure.

Recurrence free survival is an appropriate outcome measure, however, there is no evidence that it correlates with overall survival. In the clinical study report recurrence was variously defined as ‘recurrence by definitive scan or biopsy’,

'recurrence by biopsy', 'recurrence by investigator visit' and 'recurrence by CRF (case report form) documented recurrence', and sensitivity analyses were performed around these definitions (in the clinical study report (CSR)). There were no details in the submission on the effect on RFS depending on the definition of recurrence used.

Overall survival is an important outcome measure. However, due to a relatively limited risk of death from GIST in the first few years after imatinib treatment and the fact that the median follow-up time for overall survival was only 19.7 months [redacted] for significant risk group),no difference in survival is apparent at this stage. Longer-term follow-up is required to show if the two different treatment strategies (one with 1 year adjuvant imatinib, both with (400 and/or 800mg) imatinib and/or sunitinib on progression) result in a survival difference.

4.1.7 Describe and critique the statistical approach used

The statistical analysis of trial Z9001 was appropriate. The caveats described in the submission concerning the retrospective analysis of results for the significant risk subgroup were clearly explained and were appropriate.
There was only one main included RCT so meta-analysis was not possible.

4.1.8 Summary statement

All relevant studies appear to have been included in the submission.
Additional relevant data was provided in response to clarification questions on the 'significant risk' population, which forms a sub-group of the main relevant trial (Z9001) and is the population under consideration here. The submitted evidence appropriately reflects the decision problem.

4.2 Summary of submitted evidence

4.2.1 Summary of results

Recurrence free survival (Z9001 trial)

a) Total trial population

The estimated one-year RFS rate was 98% in the imatinib arm and 83% in the placebo arm (HR 0.35, 95% CI 0.22-0.53, p<0.0001). This is based on a median observation time of 14 months, and few patients were evaluable at later time-points. Median RFS had not yet been reached at the time of analysis.

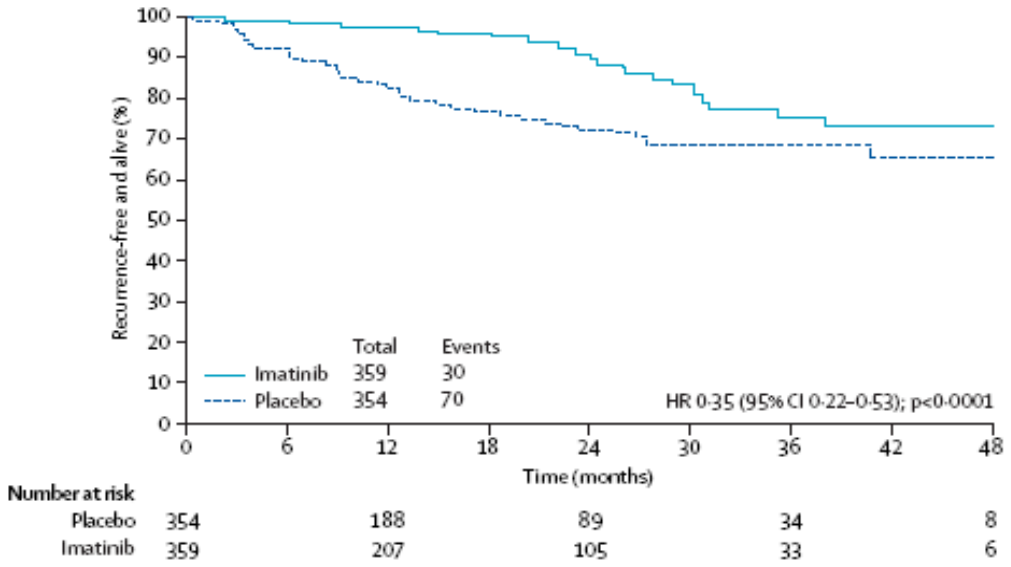


Figure 6 from submission,p43 recurrence free survival (ITT population, n=713)

The ERG notes a slight discrepancy between the above Figure 6 (p43) from the submission and the Figure 11-2 from the CSR provided by the manufacturer, see below.

Confidential information removed

At these later time-points there are very few patients contributing data, and this difference will not affect overall conclusions drawn from the data.

b) Significant risk population

The RFS probability at one year is 98.3% in the imatinib arm and 71.5% in the placebo arm.

[redacted]

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Results have not been presented in the submission according to different definitions of recurrence, so the ERG is unclear what the impact would be.

Similarly, there were no details in the submission on whether investigator or independent review data was used in analyses. It states in the short clinical study report provided by the manufacturer (p57, 11.3.8.2) that there were slightly different results from an independent review interim analysis, but we are unclear about the potential impact of this.

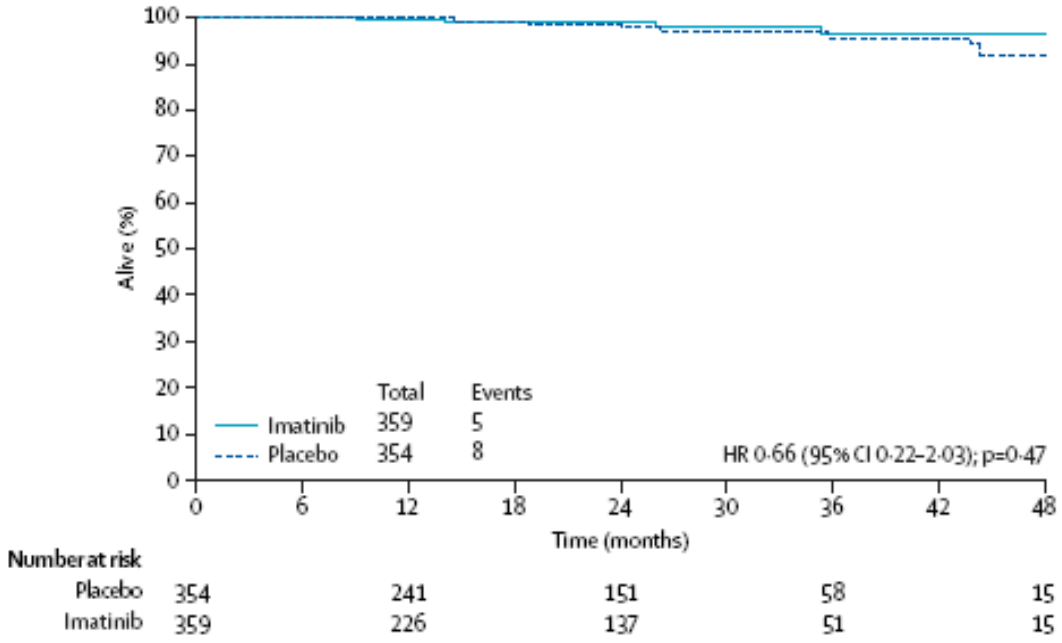
There are details in the CSR around how sensitivity analyses were performed for different ways of counting missing scan/biopsy data. No reference is made in the submission of what impact this may have on results.

Overall survival (Z9001 trial)

a) Total population

Estimated overall survival rates at two years are [redacted] in the imatinib arm and [redacted] in the placebo arm. Median follow-up time is given as 19.7 months. Again, the ERG notes the discrepancy in follow-up times for the outcome measures of recurrence free survival and overall survival, and for the total and at significant risk populations.

Figure 10 from submission p48, overall survival (ITT population, n=713)



b) Significant risk population

Estimated overall survival rates at two years are [redacted] in the imatinib arm and [redacted] in the placebo arm.

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Median follow-up time for the significant risk group for overall survival is [redacted] months. At the time of data analysis [redacted] in the imatinib group and [redacted] in the placebo group were still alive.

Data on subsequent use of imatinib

There is a small amount of retrospective data available from the Z9001 trial on patients who completed a year of adjuvant imatinib, subsequently relapsed and who were then retreated. [redacted]

[redacted].No further details were provided and the data is not in the public domain. We do not know what will happen to response rates in these patients in the long term; it is possible that prior treatment with imatinib could have an effect, with some patients for example acquiring earlier resistance to imatinib. The manufacturer states that these rates are comparable to those in patients who have not been exposed to prior imatinib. In the study by Demetri 2002, patients with advanced GIST, who received imatinib for the first time, had a 53.7% partial response rate and

an additional 27.9% stable disease rate (total 81.6% partial response or stable disease).

The ERG constructed a Kaplan-Meier plot (95% CI) (see Figure 2) using the data from the 23 patients. Eleven patients were censored as still responding at last observation. The uncertainty associated with response duration is considerable.

Figure 2 Kaplan-Meier plot (95% CIs) of time to progression with repeated imatinib

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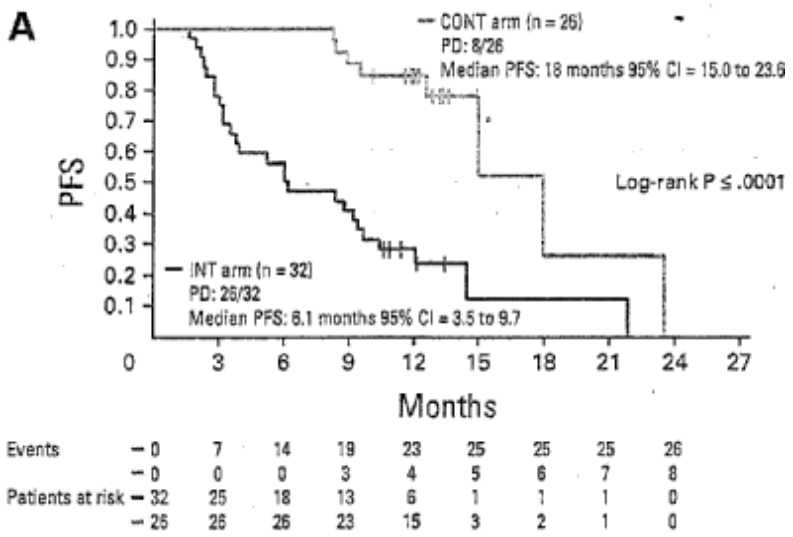
The ERG identified one further study (Blay 2007[20]), which compared continued (CONT) with interrupted (INT) imatinib in patients with advanced GIST. Although this is a different population, it addresses some of the issues of interest such as imatinib resistance with different treatment strategies. After one year of treatment, imatinib was continued in one study arm (n=26), and stopped, and restarted on progression, in the other arm (n=32). At follow-up, 8/26 (31%) in the CONT arm and 26/32 (81%) in the INT arm had disease progression. The median follow-up time was not stated. 24/26 (92%) with

progression in the INT arm responded to imatinib reintroduction. The figure taken from the publication shows progression free survival in the two treatment arms:

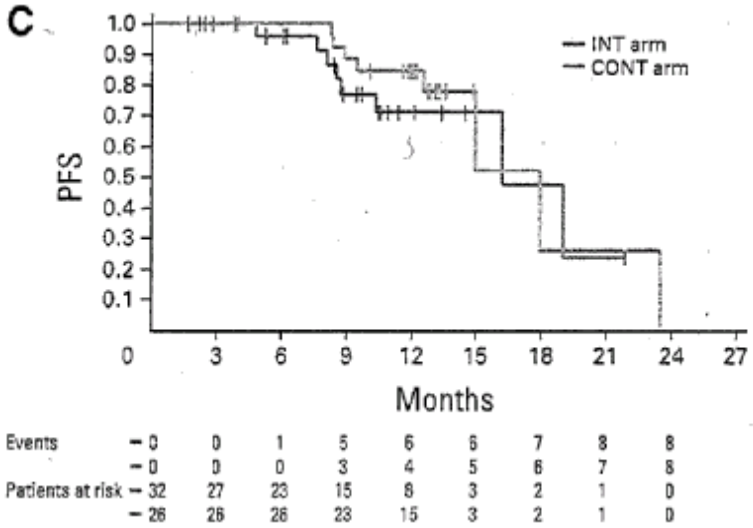
Progression-free survival with CONT or INT treatment (Blay 2007[20])



There were no differences in OS or QoL (QoL was assessed 6 months after randomisation). Due to an excess number of progressions in the INT arm, randomisation was stopped after 58 patients and it was recommended that all patients in the INT arm receive imatinib; only 2/21 non-progressing patients restarted immediately. We do not know the mean/median length of the treatment gap in the INT arm.

The incidence of imatinib resistance was similar in both arms: at follow-up 8/32 (25%) of patients in the INT arm progressed after imatinib reintroduction compared to 8/26 (31%) in the CONT arm. Sub-group analysis showed that of those with no residual disease (on CT scan), 7/19 in the INT arm and 0/7 in the CONT arm progressed. The figure below taken from the publication shows incidence of imatinib resistance:

Incidence of imatinib resistance in CONT and INT treatment arms (Blay 2007[20])



There are uncertainties surrounding these results, as the mean treatment gap in the INT arm and the median follow-up time are unknown, the study is based on small patients numbers and there are very few patients at later time-points (particularly for the sub-group analysis). Also, this trial is of imatinib in advanced GIST, rather than as an adjuvant.

Quality of life data

No quality of life data is available from the Z9001 study or any of the non-RCTs.

Adverse events

Information on adverse events in the significant risk group were provided on request. There were slightly more grade 3 or 4 adverse events in the imatinib group, and a greater number of patients with AEs leading to discontinuation or dose adjustment/interruption.

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Serious adverse events or grade 3-4 AEs were not reported separately for the significant risk group. For the total population, serious adverse events occurred in [redacted] imatinib patients and [redacted] placebo patients, in [redacted] and [redacted] patients respectively these were thought to be related to study treatment. The most common SAE was gastrointestinal effects. Five deaths occurred in the imatinib arm, [redacted]. Eight deaths occurred in the placebo arm, five of which were due to GIST. There were 31% grade 3-5 AEs in the imatinib arm compared to 18% in the placebo arm.

[redacted]

[redacted].

It is unclear if this data includes patients from the placebo group who received imatinib following recurrence.

The AEs listed appear to be consistent with what would be expected from imatinib treatment (see SPC[13] for details).

The ERG notes that a patient receiving imatinib adjuvantly will experience adverse events without any of the benefits associated with disease symptom relief, therefore the AEs might be perceived to be relatively worse compared to a patient who has active disease. This is why QoL measurements would have been useful, unfortunately no QoL was measured in the Z9001 trial.

Results from non-RCTs

Fifteen non-RCTs were included. Ten were case reports, where between 1-5 high risk patients received imatinib following surgery (at varying doses or dose not reported). Treatment lengths varied between 3 and 26 months and follow-up between 9.7 and 48 months (or not reported). The majority of patients (n=12) were recurrence free at the time of their follow-up. One had discontinued due to side effects and four had disease recurrence after stopping treatment, had restarted treatment and currently had stable disease.

There were five larger studies, described below. The majority of studies included patients classified as high risk (n=nine, using a variety of definitions), one (Li 2009) included intermediate and high risk patients, one intermediate risk patients and four did not specify risk.

DeMatteo 2008-uncontrolled

107 patients were available for analysis (number recruited not reported). Treatment was for 12 months and median follow-up was 48 months. Recurrence free survival was 94%, 73% and 61% at 1,2 and 3 years. Overall survival was 99%, 97% and 97% at 1,2 and 3 years. 19 (17%) of patients reported grade 3 toxicities.

Kang 2009-uncontrolled

47 patients were analysed (of 47 recruited).Treatment length was 24 months and follow-up was 22.6 months (not stated if median). Recurrence free survival was 97.9% and 91.6% at 1 and 2 years. Grade 3 toxicities were neutropaenia 18.8%), rash (8.3%) and diarrhoea (2.1%). Grade 4 toxicities were neutropaenia (4.2%) and pruritis (2.1%).

Zhan 2006-uncontrolled

51 patients were analysed (of 57 recruited); 43 had completed 12 months of imatinib treatment. Recurrence free survival was 96% at approximately 1 year. 58% had adverse events.

Li 2009-non-randomised, controlled

56 patients (of 56 recruited) were given imatinib for 12-36 months (median treatment duration 20 months). 49 patients (of 49 recruited) were given no treatment following surgery. There are no details on how patients were selected for treatment/no treatment arms. Median follow-up was 30 months. Recurrence free survival was 100% and 94.4% at 1 and 2 years in the adjuvant imatinib arm and 89.8% and 60% at 1 and 2 years in the control arm. Adverse events were not reported.

Nilsson 2007-historical control

23 patients (of 23 recruited) were given imatinib for 12 months. These were matched with 48 historical controls (matched for tumour size, maximal proliferative activity with Ki67 antibodies (Ki67 max%) and R0 resection) who were given no treatment following surgery. Mean follow-up was 40 months (18-62) in the imatinib group and 36 months (2-151) in the control arm. Disease recurred in 1/23 in the imatinib arm (22 months after termination of imatinib) and in 32/48 in the control group. Recurrence free survival was 100% at 1,2 and 3 years in the imatinib arm and approximately 75%, 47% and 40% at 1,2 and 3 years in the control arm (read off graph by ERG). Adverse events were not reported.

One additional abstract was provided to the ERG in response to clarification queries:

Nishida 2009[18]-uncontrolled

64 high risk patients received imatinib for 12 months post surgery. 49 (77%) patients completed 12 months of treatment. 15 (23%) patients did not complete due to relapse (n=2), toxicities (n=10), and consent withdrawal

(n=3). At a median follow-up of 109 weeks (25.4 months), 20 patients had experienced relapse and the 3-year relapse free and overall survival rates were 59% and 87%. 19 (30%) patients had grade 3-4 AEs, including neutropaenia (13%) and hypophophataemia (6%).

Comment on non-RCTs

These studies confirm that adjuvant imatinib delays recurrence of disease. Recurrence free survival estimates in patients given adjuvant imatinib are similar to those in the Z9001 trial, though the rates in Nilsson 2007 are very high, with 100% of patients recurrence free at 3 years. Recurrence free survival in the control arm is lower in the Nilsson study compared to the Z9001 trial, however the patients in Nilsson are all at high risk of recurrence. Patient numbers in Nilsson are small and results subject to uncertainty. Only one study looked at overall survival (DeMatteo 2008); follow-up was for three years. We do not know how many patients were at risk at year three.

Treatment durations were longer than 12 months in Li 2009 (median of 20 months) and Kang 2009 (24 months); follow-up was 30 months (median) in Li 2009 and 22.6 months in Kang 2009. The ERG notes that these studies were used to provide justification for a maintained treatment effect of adjuvant imatinib given beyond 12 months for the economic model. The model base case assumes three years of adjuvant therapy.

4.2.2 Critique of submitted evidence syntheses

The submission is based mainly around one RCT, the Z9001 trial.

The population relevant to this appraisal is a sub-group of patients with significant risk of recurrence. Assignment of risk level was done retrospectively and only 78% of patients were categorised according to risk. There is therefore a possibility of imbalances at baseline (see section 3.1) and risk of bias. The trial was not powered to show differences for this sub-group.

There is some uncertainty around how missing data was handled and which definition of recurrence was used for the analyses in the submission, and the possible impact on results. There are some slight discrepancies between the DeMatteo publication and the submission, for example in median follow-up times and the figures presented. Follow-up times are different for recurrence free survival and overall survival and for total population and the significant risk population and there are no details on why there are discrepancies.

The data from the trial is very immature as follow-up times are short [redacted] for recurrence free survival for the significant risk group and [redacted] for overall survival) and data at later time points is based on few patients at risk. There is no evidence to show that adjuvant imatinib given for one year prolongs overall survival. Median overall survival estimates have not been reached in either treatment arm.

The ERG notes that there is no data from the Z9001 trial on the effect of giving adjuvant imatinib for three years, however, this is what the base case in the economic model assumes. Data from two non randomised studies are provided to inform this estimate (Li 2009 (median of 20 months treatment) and Kang 2009 (24 months treatment)), although treatment lengths also fall short of three years, and there is no information on overall survival from these studies.

There are no data on resistance to imatinib with long-term use. Studies suggest that in the short term similar responses are achieved with subsequent treatment with imatinib compared to 1st time treatment with imatinib, however this is based on small patient numbers and there is no long-term follow-up.

4.2.3 Summary

The evidence is based mainly on data from a sub-group of one RCT and is possibly at risk of bias. There are some uncertainties around the analysis of the data, nonetheless there is clear evidence that one year of adjuvant imatinib delays disease recurrence. Overall survival was similar in both treatment arms. The data is immature with median overall survival not reached in either treatment arm. There is no good long-term evidence on recurrence rates (resistance) when imatinib is given repeatedly.

5 ECONOMIC EVALUATION

5.0.0 Description of manufacturer's search strategy and comments

Summary from the manufacturer's submission:

The following sources were searched in June 2009: Cochrane Database of Systematic Reviews (CDSR) (Wiley); Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley); Database of Abstracts of Reviews of Effects (DARE) (Wiley); HTA Technology Assessment database (HTA Database) (Wiley); Economics Evaluation Database (EED) (Wiley); EMBASE (Ovid) 1980 to search date; MEDLINE (Ovid) 1950 to search date; MEDLINE In Process (Ovid) 11 June 2009; Science Citation Index (Web of Knowledge) 1900 to search date; Social Science Citation Index (Web of Knowledge) 1900 to search date. No date or language restrictions were applied [see comment below]. Citation searches of key references were performed on Science Citation Index via Web of Knowledge.

Comments:

- Although it is stated that no date restrictions were applied to the searches, those of CDSR, DARE, HTA database, EED and CENTRAL appear to have been restricted to 1991 to 2009.
- Only the search strategy for MEDLINE is reported; it is stated that 'the search was adapted for the other databases'. However, without more explicit information it is impossible to verify the search strategies for the other databases.
- The search strategy for MEDLINE appears to be sound and is unlikely to have missed references.

5.1 Overview of manufacturer's economic evaluation

The manufacturer's model simulates transitions of two hypothetical cohorts of 1000 patients diagnosed with primary GIST

- Patients treated with surgical resection only
- Patients treated with surgical resection followed by adjuvant imatinib therapy

The model contains ten health states: no recurrence and no treatment; no recurrence and imatinib adjuvant therapy; post recurrence and 400mg imatinib; no recurrence and completed imatinib adjuvant therapy; post recurrence and 800mg imatinib; dose escalation to 800mg imatinib; sunitinib second line treatment; BSC; death GIST; and death other.

Effectiveness data is contained in tables 14-20 of the submission (p68-71). The model assumes adjuvant therapy is given for three years. Recurrence rates are taken from the trial data and extrapolated (the recurrence rate from the first year of ACOSOG Z9001 was applied for the first three years plus a further six months following the end of the imatinib treatment period).

Data on utilities was not collected by the manufacturer and the utility values included rely heavily on an earlier phase three clinical trial of sunitinib compared with BSC. Four assumptions are highlighted in the submission:

GIST patients who are surgically resected and recurrence free have the same utility as healthy individuals; utilities associated with disease states were multiplied by age specific health utility values; utility following dose escalation on imatinib is assumed to be the same as utility on sunitinib treatment; and patients experiencing adverse events resulting in discontinuation are assumed not to experience a utility decrement.

Cost data was taken from a range of appropriate sources with estimates of resource use based on the trial data, relevant clinical guidelines and literature. Unit costs are partially reported in Tables 18-20 (p70-71 in submission) but not costs per cycle per health state. Two assumptions are made within the costs: costs of continuing phase of cancer are estimated assuming, on average, two GP visits per year, five outpatient visits per year and 0.5 CT scans; and the onset cost of recurrence is assumed to include one GP visit, one CT scan, and for those suitable for resection, the cost of surgical resection of the tumour or distant metastases.

The model's cycle length is one month. PSA was undertaken on the base case and multiple one way sensitivity analyses were conducted, with additional analyses carried out as part of the clarification process.

5.1.1 Natural history

The model structure used by the manufacturer reflects reasonably the natural history of the disease. The manufacturer's Figure 13 (p66 in submission), reproduced below, shows the model pathways and the possible transitions between health states. The model has been designed to estimate the costs and effects of treatment over a lifetime time horizon and runs for six-hundred, one month cycles. Sensitivity analysis was undertaken using a five year time horizon.

The only two terminating states in the model are death from GIST and death from any other cause. Mortality is estimated using a combination of the trial data and estimates from the literature. Although the data from the trial patients is limited to just one year, the base-case analysis for the economic model assumed a three year treatment duration, with the effectiveness for years two

and three assumed to be the same as for year one. Overall survival was estimated from the trial data and the literature; the appropriateness of the model fit is discussed in Section 5.1.4 of this report. Re-analysis of the base-case scenario of the economic model using an alternative estimate of survival was not possible, given the limitations of the evidence presented by the manufacturer. A one year treatment duration scenario is tested in the manufacturer's own sensitivity analysis.

The ERG notes that there may a small group of patients who do not get imatinib then sunitinib on recurrence, but, for various reasons, may move directly to sunitinib or BSC. This possibility is not accounted for in the model.

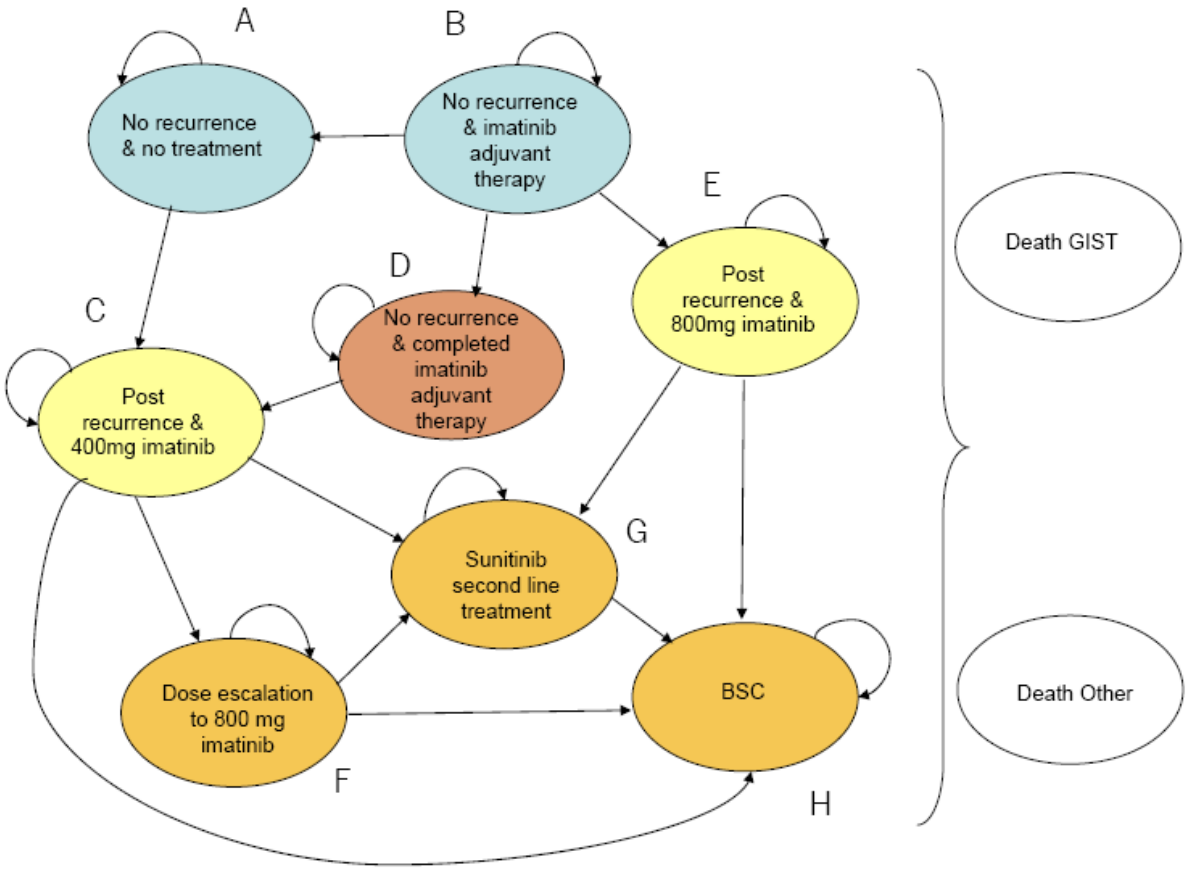


Figure 3: Transition Pathways in the Model

5.1.2 Treatment effectiveness within the submission

Treatment effectiveness came from the double blind RCT Z9001 looking at one year of imatinib adjuvant therapy versus no therapy. This trial demonstrated clearly that for the whole randomised population (n=713) adjuvant therapy significantly delayed recurrence of disease (hazard ratio 0.35, 95%CI 0.22 to 0.53).

The economic model is concerned with patients at significant risk of recurrence. In the Z9001 trial significant risk patients represented a subgroup. Z9001 patients in this subgroup were identified by retrospective analysis using criteria devised by Miettinen et al 2006[5]. Of 713 randomised patients 566 were available for this analysis and of these 302 were identified as at significant risk, 154 allocated imatinib and 148 allocated placebo. There were some moderate imbalances in baseline characteristics between these groups (tumour site and performance status).

In the base case the economic model considers three years adjuvant therapy so that the model requires assumptions regarding the response of patients to adjuvant administration from year one to three.

5.1.3 Health related quality of life

The manufacturer did not collect data on health-related quality of life during the trial using an appropriate preference based instrument such as the EQ-5D. Estimates of utility in the model were instead taken from published sources in the literature or were assumed by the manufacturer (Table 17 from submission, p69). Utilities associated with disease state were multiplied by age-specific healthy utility values.

Table 17 from submission: Utility of health states

	Mean	*SD*	*Distribution*	*Source/Comments*
Health State				
Recurrence-free	1.0	-		Assumption
Recurrent GIST (1st recurrence)	0.875	0.2		2003 Novartis NICE submission for metastatic GIST[58]
Recurrent GIST (2nd recurrence)	0.71	0.2		Chabot et al 2008 – Based on health state: "On sunitinib treatment, no progression" [59]
			Beta	
BSC	0.577	0.3		Chabot et al 2008 – Based on health state: "Progression" [59]
Age specific health utility values	-	-		Ara and Brazier 2009[60].

It was not clear from the original submission how the values used in the economic model were identified and selected. Although a systematic review was undertaken, no inclusion or exclusion criteria were specified in section 10.3 (Appendix 3, p142) of the submission. Thirty-three studies were excluded by the manufacturer in the review of quality of life evidence and reasons for their exclusion were provided. Given the time constraints of the STA process, it was not possible to review all of these studies to determine whether their exclusion was appropriate. Additionally, no alternative values were identified in the submission so it is not clear whether these values represent the most methodologically robust values or simply the values favoured by the manufacturer for their analysis.

The primary evidence source for utility values used in the submission is a study by Chabot et al. 2008[21] (ref 59 in the submission). The aim of the Chabot study was methodological and not clinical. The study design was based on a model submitted to the Canadian Agency for Drugs and Technologies in Health Common Drug Review (hereafter, the CDR) for the approval of sunitinib for treatment following failure or intolerance of imatinib. The source of utility estimates in the Chabot study was a phase three clinical trial of sunitinib compared with BSC. Chabot highlights the sensitivity to the results of changes in the utility estimates. Furthermore, they advise caution in interpreting the results due to this uncertainty. No disutility was applied for

AEs, which seems unreasonable given that AEs (including some resulting in discontinuation) are likely to occur with adjuvant treatment.

Utility values of less than zero were not modelled and the justification for this is that the health state of progressive disease reflects an average of a cohort of patients. Nevertheless, if the use of the mean is valid in a deterministic context, the range is needed for a probabilistic analysis. There is a level of uncertainty related to that assumption that should be taken into account within the model. It seems likely that in this group of patients there is a real, if small, probability that a patient might experience the treatment and illness as a state worse than being dead.

Figure 4, Figure 5 and Figure 6 are histograms that demonstrate how this may be the case (note the variable ranges of the Y-axes). These figures show the results for 2,000 random draws from a beta distribution estimated using mean and standard deviations for each of the utility estimates used in the economic model (where appropriate estimates of uncertainty were provided by the manufacturer). The red lines running vertically through the figures demarcate the median value as well as the top and bottom deciles.

It is evident that patients receiving best supportive care have a small but realistic chance of having a negative utility. It is less likely that patients in recurrence will have a negative value, but still possible. Given the high interpatient variability acknowledged by the manufacturers the omission of this possible outcome from the economic model is unacceptable. Given the constraints of the Single Technology Appraisal process it has not been possible for the ERG to modify the model to test the implications of taking the more appropriate approach.

Even if this omission could be rectified by the ERG, the manufacturer is inconsistent in its justification for not modelling the potential for negative utility values. On the one hand the claim is made that because the mean value is relatively close to one it is unlikely that values below zero will occur. On the other hand, it is clearly stated in the response to clarifications that the standard deviations of the utility values reflect high interpatient variability. The

first statement suggests it is not necessary to have modelled potential negative utility values, the second clearly identifies why it would have been important to do so.

Figure 4: Histogram of 1st Recurrence utility value (Mean=0.85, SD=0.2)

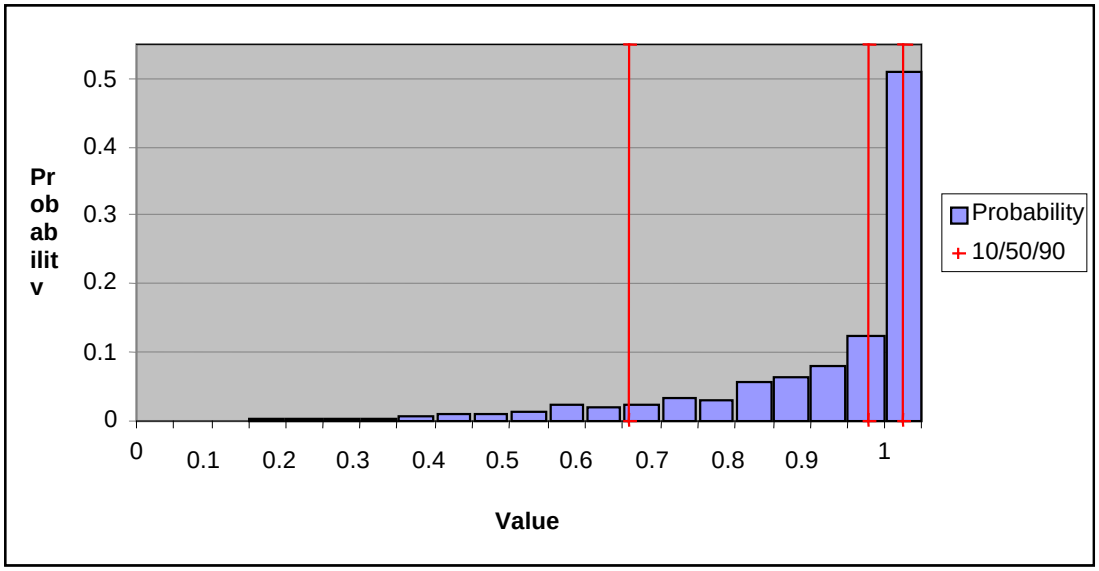


Figure 5: Histogram of 2nd Recurrence utility value (Mean=0.71, SD=0.2)

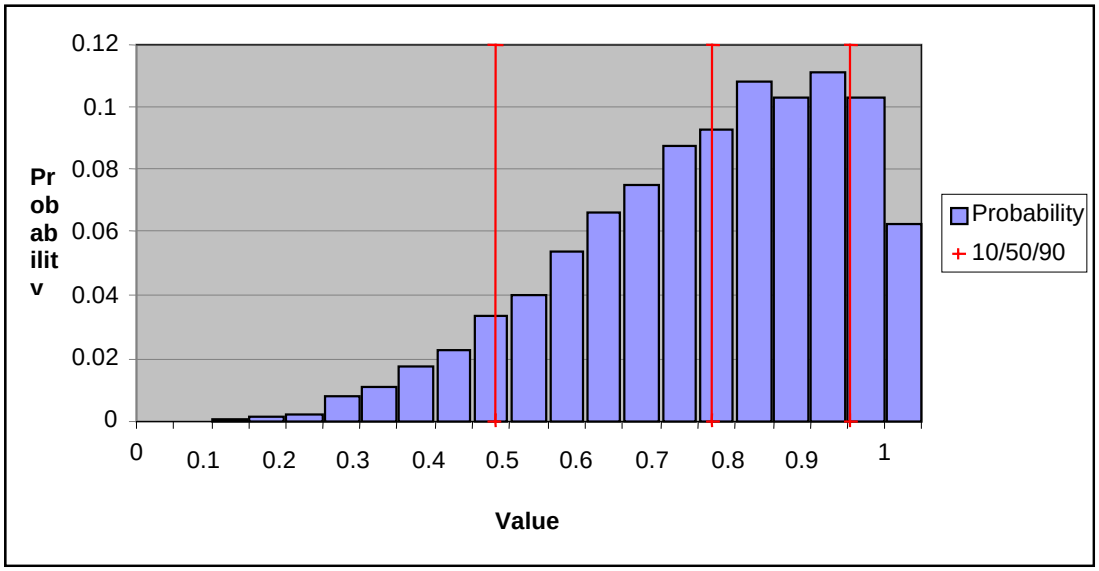
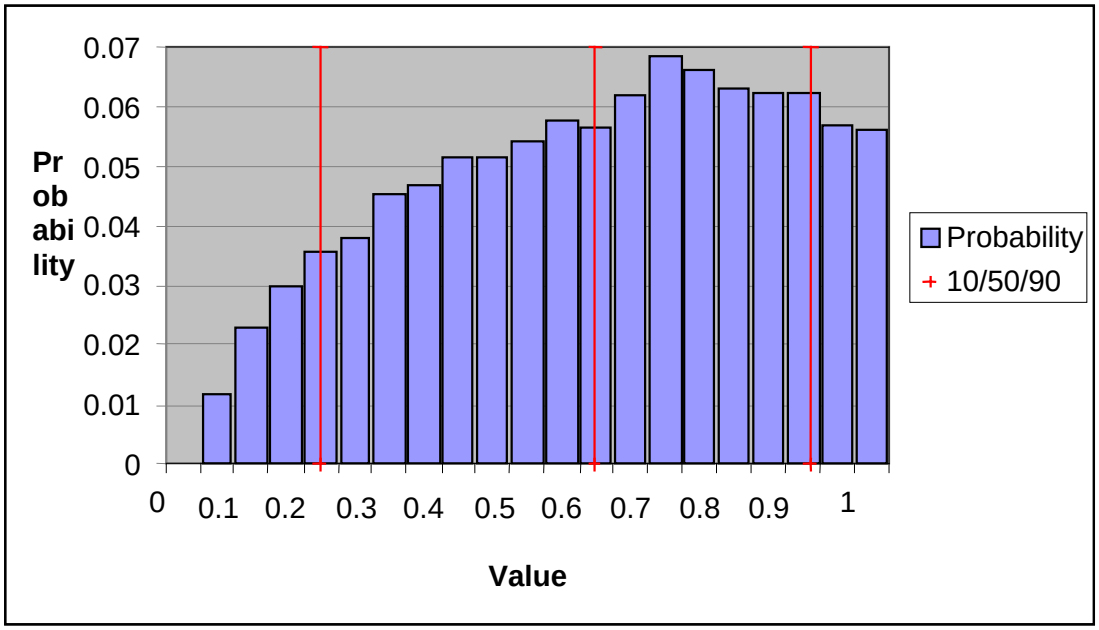


Figure 6: Histogram of BSC utility value (Mean=0.577, SD=0.3)



It is also the case that the model includes no estimate of uncertainty associated with the recurrence free health state. No justification for this omission is provided though it seems likely that this is because it is an assumed value and not a reflection of the actual clinical population. It is unlikely that the mean estimate is the true estimate of benefit for all patients and the uncertainty in this value should have been included in the economic model as a basic component of the probabilistic analysis. As a result, this is likely to be an overestimate in the benefit received by patients. This overestimate has the effect of favouring the novel treatment, as, according the to the manufacturers' estimates, more patients remain in the recurrence free health state following treatment with imatinib than those who do not receive the treatment. Unfortunately, due to the design of the economic model in Excel the ERG are unable to make changes to the values used to test the effects of changes in this assumption. The executable model was not built with the end-users needs in mind; changes in parameter values cannot be introduced as it is unclear if such changes are appropriate given the model structure and complexity.

In the model pathway patients can transit from state B to state A due to adverse events. The other reasons for withdrawal are not explicitly included in

the model. Nevertheless, we question whether there are cost and health related effects related to that assumption that are not included in the model. In particular, what effect would this have in estimates of utility values.

As part of the clarification stage of the appraisal we asked the manufacturer for further details on how the utility values were applied in the model with respect to the age adjusted utility values. In each case, the health state utility values were multiplied by the age adjusted utility value. So for a patient in full health (utility =1.00) this would be multiplied by the age adjusted value (for a 58 year old male this is equal to 0.8454) giving the total utility for a patient of a given age in a given health state (in this example, 0.8454). A 71 year old male patient in the 1st recurrence health state would have a mean health state utility of 0.875. After applying an age adjustment of 0.7863, this would give an overall utility score of 0.688 (0.875*0.7863).

Although this approach may be appropriate for patients assumed to be at full health, it is not suitable for patients in other health states. As no self-reported health related quality of life was collected by the manufacturer, they chose to assume that patients who were recurrence free had otherwise perfect health (the validity of this assumption is addressed below). This was then adjusted to population norms for people in otherwise good health. This is approach is conceptually and methodologically sound.

However, when applied to patients in health states other than no recurrence it is not conceptually sound or methodologically appropriate. Again, as primary data was not collected by the manufacturer, patients in these health states have been assigned utility values. However, for these additional states, the values are taken from the literature and based on self reported health related quality of life using the EQ-5D instrument. These values will already include the relative effects of age, as they have been determined using an age appropriate population of patients with recurrent GIST to answer the EQ-5D and then assigning the appropriate utility as valued by the general population. By further reducing the utility score according to the age of the patient, the manufacturer is suggesting that the patient is unaware of their own age when assessing their own health.

The result of this approach is likely to underestimate utilities for patients in states other than no recurrence. It is not possible to separate the effect of recurrence from the age adjusted utility figures. The effects of this problem are likely to be small, but would favour the manufacturer if more patients spend time in the recurrence states under BSC than with imatinib treatment.

This approach could also lead to an overestimate of utility values as the assumption of otherwise full health for patients with no recurrence may be optimistic. Even patients without recurrence are likely to experience some decrement to utility; for example, anxiety about recurrence is widespread amongst patients in remission. Even the application of age adjusted decrements to all health states using general population health values does not adjust for this, as it is the assumption that health is unaffected by previous treatment, anxiety or any other aspect of the condition that is in question.

The estimates of utility used by the manufacturer may not reflect the patient population of the study. The values taken from the Chabot[21] study were originally derived from a study of sunitinib in patients resistant to or intolerant of imatinib. There is no data in the study that values the health benefits of imatinib. While there is a *prima facie* case for accepting that a health state for recurrence would be valued similarly no matter the treatment being used, this approach fails to capture the disutility associated with potentially severe side-effects of treatment with imatinib (see section 4.2.1 for adverse events). This also applies to those patients receiving imatinib but that remain free of recurrence. Any side effects of treatment will not be captured in the health state valuation leading to a potential overestimate of utility in this group of patients.

Following from the numerous flaws in the modelling of health state utility identified above and given the lack of any reliable evidence included in the submission relating to the value of health states while being treated with imatinib, the results of the submission should be interpreted with caution. Not only is the accuracy of the estimated benefit of the treatment in terms of QALYs highly likely to be inaccurate, the model does not allow us to even estimate in which direction these are likely to be wrong.

5.1.4 Survival and progression

Overall survival was estimated from the trial data and the literature. The literature sources and resulting monthly probability (MP) of death were presented in Table 16 (page 69) of the submission, this was revised after request for clarification and the revised version is reproduced below.

Updated Table 16 : Monthly Probability Of Death Following GIST Recurrence

		Mean	*SD*	*Distribution*	*Source/Comments*
Best Supportive Care	health state H	0.0432	0.0051	Beta	Huse et al 2007[55], Tran et al 2005[56], Demetri et al 2006[54]
Imatinib 400 mg/day	health state C	0.0135	0.0053		Verweij et al 2004[52]
Imatinib 800 mg/day	health state E	0.0125	0.0051		
Imatinib 800 mg/day for second recurrence	health state F	0.0373	0.0131		Demetri et al 2006[54]
Sunitinib second-line treatment	health state G	0.0373	0.0131		
Death due to non-GIST causes	all health states				Published government life tables UK[57]

Reference numbers refer to submission

Comment

- A single MP of death was applied for all states beyond states A, B and D irrespective of whether the patient arrived in these states after adjuvant therapy (AT) or no therapy (NAT).
- This also applies to recurrence and discontinuation rates (see below)
- The model supplied to the ERG did not allow separate input for these states according to treatment arm
- It appears that the MP of death for second recurrence on 800mg imatinib is assumed to be the same as that for sunitinib second line treatment; this appears to be taken from Demetri et al 2006[9] in which patients were imatinib resistant at entry.

The method for calculation of these monthly probabilities was described in Section 7.2.12.1 of the submission, which is reproduced below:

From the submission:

> 7.2.12.1.
>
> Annual probabilities from the data were transformed into monthly rates using the formula -LN(r)/t, where r is the recurrence rate and t is the time interval (i.e., 12). Monthly rates were converted to monthly transition probabilities using the formula 1-e-r.

Comment

Unless the survival time relationship is exponential the calculation of monthly probability will be influenced by the value of t used. The implication of "*t is the time interval (i.e., 12)*" above may be that annual rates were used, however this was not always the case (see below) and the general approach lacked explanation.

Because it was not easy to see how these monthly probabilities had been derived from the literature and because of the type setting error in the calculation formula (probability formula should read: 1 – exp(-r)), the ERG requested clarification.

The manufacturer's clarification responses merely referred to a hidden sheet in the Excel model termed "Rate conversions". This sheet is reproduced below:

From the manufacturer's model

	Orignal Metric	Monthly Probability				
Rate/Prob of Progression				original rate	months	
Imatinib 400mg	PFS - 44%, 2 year	0.03362906	Verweij et al., 2004	0.44	24	
Imatinib 800mg	PFS - 50%, 2 year	0.028468059	Verweij et al., 2004	0.5	24	
Sunitinib	PFS - 24.1, weeks	0.108674123	Demetri et al., 2006	0.5	6.025	
Rate/Prob of Death						
Imatinib 400mg	OS - 85%, 1 year	0.013451947	Verweij et al., 2004	0.85	12	
Imatinib 800mg	OS - 86%, 1 year	0.012489919	Verweij et al., 2004	0.86	12	
Sunitinib	OS - 73 weeks	0.037268447	Demetri et al., 2006	0.5	18.25	
BSC						
Huse	OS - 20 months	0.034063671	Huse et al., 2007	0.5	20	
Tran	OS - 77%, 1 year	0.021544917		0.77	12	
Demetri	OS - 36 weeks	0.074125288		0.5	9	
		0.043244625				
Discontinue due to AEs						
Imatinib 400mg	7%	0.002900205	Verweij et al., 2004	0.07	24.986	(median follow-up)
Imatinib 800mg		0.002900205	Verweij et al., 2004	0.07	24.986	
Sunitinib	9%	0.049935398	Demetri et al., 2006	0.09	1.8411	(median time on drug)
Discontinuing Sutent		0.158609521	Demetri et al., 2006			
Imatinib 800 for 2nd recurrence	PFS - 5.28 months	0.123025949	Contreras-Hernandez et al., 2008	0.5	5.28	
	Discontinuing	0.125926154	Verweij et al., 2004			

Comment

Conversion from the "*Original Metric*" column to "*months*" column is inconsistent and differs depending on whether the original metric is years or weeks, thus: years to months is based on 1 month = 365.25/12 = 30.44 days; weeks to 1 month is based on 1 month = 4 weeks = 28 days.

In the "Original Metric" column this sheet does provide information about what data was extracted from the references, and the monthly probabilities have been calculated using the procedure in section 7.2.12.1. except that " *t* " is not consistently 1 year. The submission and clarification response completely lacked details of the studies such as study design and the number and selection of participants; similarly no specific information could be found about how data extraction was performed. Thus it is unclear how or why these

particular studies were selected and what rules (criteria) may have been employed for their data extraction.

Monthly probability of death (BSC)

The ERG briefly examined the listed primary literature sources used for the calculation of monthly probability of death in the BSC state (see Table 3). This was done in an attempt to ascertain the data extraction procedure(s) used and to verify the monthly probability of death provided in the model sheet. The manufacturer used three studies: a large retrospective analysis (Tran et al 2005[22]) of all patients in the USA given a diagnosis of GIST between 1992 and 2000 (N=1458); an RCT, Demetri et al 2006[9], examining efficacy of sunitinib in unresectable c KIT +ve imatinib-resistant patients (N=105 given placebo); an economic analysis (Huse et al 2007[23]) which stated that survival estimates were based on data from Demetri et al 2002[7] using 52 months follow up in a trial of imatinib in patients with unresectable c KIT +ve advanced GIST; this trial lacked a BSC control group and so the survival of the subgroup of 102 patients who withdrew from imatinib was used.

Table 3 Sources of monthly probabilities of death

STUDY	DESIGN	Number analysed	Data used for calculation of monthly probability of death	Comment
Tran 2005[22]	Retrospective analysis of Registry data	1,458	% alive at 1 year (timed from diagnosis to death)	Method does not censor for patients alive beyond cut off. Population an intermix of GIST and other mesenchymal tumours
Demetri 2006[9]	RCT of sunitinib v placebo in imatinib resistant nonresectable patients.	105	Median survival from Kaplan Meier plot	Estimate of median survival associated with considerable uncertainty. Some patients received sunitinib after cross over.
Huse 2007[23] *	Economic study. Survival from trial data	102	Median survival estimated from a Weibull parametric fit to observed survival.	An exponential assumption applied to a Weibull fit. Patients were those who withdrew from imatinib treatment.
* based on 52 months follow up in the Demetri 2002 uncontrolled trial of imatinib for unresectable metastatic GIST				

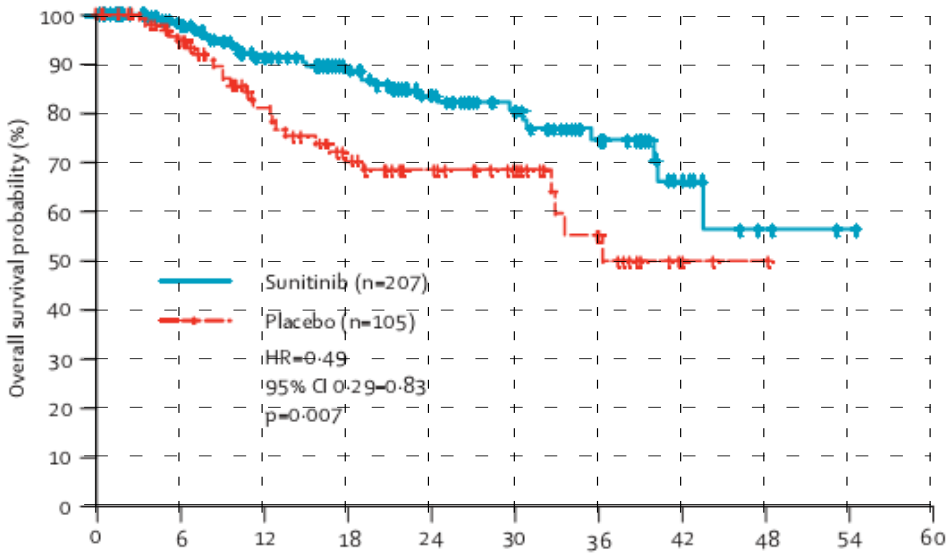
The populations in these studies varied considerably. The large US study included patients listed as having 26 different classifications of mesenchymal GI-associated tumours. Although the majority of cases may have been c-KIT +ve (and therefore “GIST” by more recent criteria) the population was inevitably complicated by the presence of non-GIST tumours. Patient survival was estimated from the time of diagnosis whereas the other two studies

estimated survival from the time of entry into trials and looked at patients who were imatinib resistant.

To calculate monthly probability of death from the Tran study[22] the tabulated 1 year overall survival for all participants was used (77%). Applying the method described in section 7.2.12.1 a monthly probability of death of 0.0125 is obtained. Tran also tabulated the 5 year survival value (38%) and this generates a somewhat higher probability of 0.016.

Using Demetri et al 2006[9] the model sheet lists a BSC median survival of 36 weeks. The ERG could not find a corresponding statement in the publication. However a Kaplan-Meier plot for BSC overall survival was published (no time unit) and is reproduced below with a grid over-layered for convenience.

Kaplan-Meier for overall survival with BSC (Demetri 2006[9])



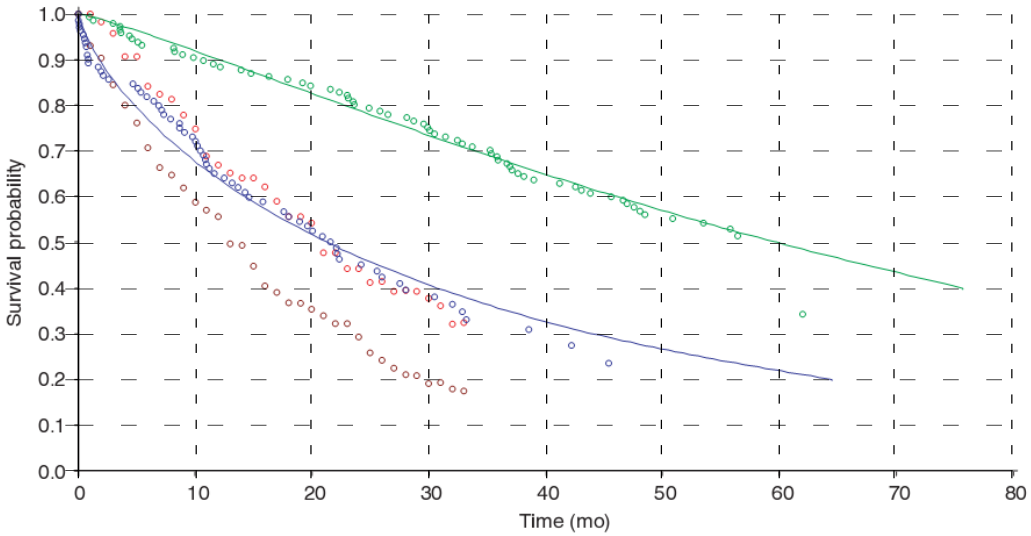
Number at risk											
Sunitinib	207	167	117	97	71	50	31	11	3	1	0
Placebo	105	85	57	43	31	22	13	3	1	0	0

From this it is evident that the 36 week median survival was obtained from this K-M plot. At this time only 13 patients remain at risk and the estimate must be associated with considerable uncertainty. If 36 weeks is taken to be 9 months

(i.e. 1 month = 4 weeks = 28 days) then the monthly probability of death calculates to 0.074 (as shown in model sheet). If 1 month is taken to be 365.25/12 days = 30.44 days then 36 weeks is equivalent to 6.899 months and the monthly probability of death becomes 0.0956. Since some patients in the placebo arm crossed over to sunitinib the estimated survival may be optimistic for the placebo group. The model sheet lists median survival for the sunitinib arm as 73 weeks which appears inconsistent with the time axis of the K-M graph.

Using the Huse et al 2007[23] economic study the model sheet lists a median overall survival of 20 months and monthly probability of death of 0.034. Huse et al fitted Weibull distributions to the observed survival of imatinib-treated and imatinib-withdrawing patients from the trial of Demetri et al 2002. The published fits are shown below with a grid over-layered for convenience. The Weibull parameters were not published but were available on request.

Weibull curves fitted to observed survival of (Demetri 2002[7])



The lower fitted curve corresponds to the group taken to be reasonably representative of BSC patients. The median survival from this Weibull curve is close to (but slightly greater) than 20 months (the value in the model sheet). It is possible the Weibull shape parameter is close to 1 in which case this curve is exponential and the calculation using the method in section 7.2.12.1. holds.

The ERG found the shape parameter to be considerably less than 1 (about 0.76). Thus the use of the Weibull fit may have been inappropriate.

Thus the three studies used to extract data for estimation of monthly probability of death differed in the way data was presented in the primary study. In Tran patients were diagnosed between 1992 and 2000 and study cut off for survival analysis was December 2000. Tran reported the observed % patients alive at 1 and 5 years after diagnosis; this analysis presumably has no censoring of patients who had survived for less than these times at cut off, as would be the case in a Kaplan-Meier estimate. A Kaplan-Meier estimate of median survival was used from the Demetri 2006 study, while for the Huse 2007 study a Weibull parametric fit to observed survival data was used.

For the BSC group the calculated monthly probability of death values have been combined giving equal weight to each; the range in the calculated monthly probability from these varies 3.5 fold and it is not clear if this uncertainty has been taken into account in the PSA undertaken.

Other monthly probabilities (MP) in manufacturer's model sheet

For imatinib groups (400mg and 800mg regimens) MP of death was taken from data in Verweij et al 2004[24] which reported the 1 year and 2 year overall survival for both groups (see Table 4 below). MP of death calculated according to one year and two year values are very similar (implying an exponential survival time relationship).

Table 4 Monthly probabilities of death following GIST recurrence

	Overall survival reported		MP of death based on 1 year data	MP of death based on 2 year data
Imatinib group	1 year	2 year		
400mg	85%	69%	0.013452	0.015461
800mg	86%	74%	0.0124899	0.0124676

MP of death for the sunitinib group is given in the model sheet as 0.023726. This can be derived from a median survival of 73 weeks (the "original metric" column) with the assumption that 1 month = 28 days. If 1 month is taken to be 30.44 days (365.25/12) the MP death becomes 0.04. On examination of the

Demetri et al 2006 publication the ERG were unable to confirm the median survival value of 73 weeks. The authors state "*a median overall survival value could not be calculated".* The time axis of the published K-M plot only extends to 54 weeks, at which time a single patient remained at risk (see figure above).

MP of progression imatinib groups was based on Verweij et al 2004[24] who reported 44% and 53% progression for 400mg and 800mg groups at 2 years. The model sheet uses an incorrect value of 50% for the 800mg group. MP of progression for sunitinib was calculated from 24.1 weeks median time to progression reported in Demetri et al 2006. This converts to MP of 0.01087 (model sheet) or 0.0118 depending whether 1 month is taken as 4 weeks or 30.44 days.

Summary of monthly probability estimates in model sheet

In summary the manufacturer provided no justification for the particular data sets used to calculate monthly probability of death or of progression. The choice of studies and methods used remain unexplained, there are apparent errors and inconsistencies, and the values applied in the model appear to be fairly arbitrary and consequently should be viewed with some caution.

Monthly probability of first recurrence

Table 14 of the submission listed the monthly probability of first recurrence in the two arms for years 1 to 5+. Shown below is the corresponding table input taken from the model input sheet.

From manufacturer's model:

Monthly Rate of GIST Recurrence		
	Rate of GIST Recurrence	
Year	Surgical resection only	Adjuvant imatinib
Year 1	[redacted]	[redacted]
Year 2	[redacted]	[redacted]
Year 3	[redacted]	[redacted]
Year 4	[redacted]	[redacted]
Year 5	[redacted]	[redacted]

How these MPs were derived was not clearly described other than that observed data from Z9001 trial was used. The ERG presume that the Kaplan-Meier plot for the significant risk group shown on page 33 of this report was used. From this K-M plot the ERG were able to replicate the year 1 and year 2 values for the surgery-only group. In the model base case for the surgery-only group the MP for year two is carried forward for years 3, 4 and 5+.
The MP for year one of the adjuvant arm is tabulated as 0.0006289. This corresponds to 0.9925 patients being recurrence-free and alive at 12 months; this value was difficult to confirm from the K-M plot because it represents such a small reduction in the proportion of recurrent free patients. In the absence of trial data for adjuvant therapy beyond 1 year this value was carried over to model years 2 and 3 of adjuvant therapy in the base case.

The submission states that the delay in recurrence from 1 year of treatment extends for six months beyond the treatment period. This assumption was also adopted for modelling three years of AT. Thus for year 4 of the adjuvant arm the MP of year 3 [redacted] was applied for the first six months and for the second six months of year 4 an MP equal to that for year 1 of the placebo arm was applied [redacted] For year 5 of the adjuvant arm onwards the MP for year two of the placebo arm was used.

Comment:

- A series of complex assumptions have been used in order to model first recurrence for years where no trial data was available.

Several sensitivity analyses (11 to 14) were conducted around these MPs. The submission provided graphical displays of the modelled recurrence for these (Figures 15 to 18, p85-88 of submission) but unfortunately not for the base case. The ERG figure below shows the base case model of first recurrence to year 5.

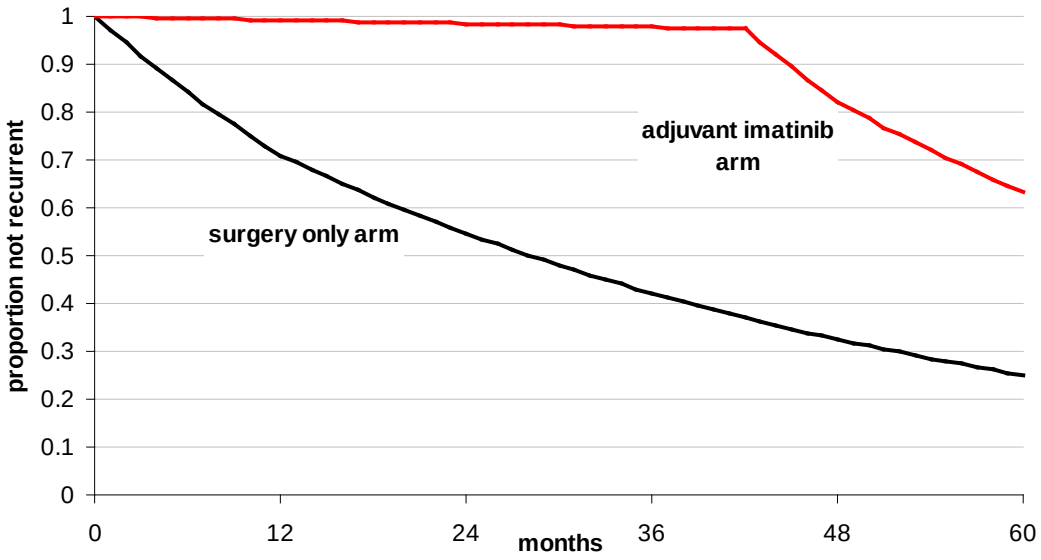


Figure 7 Base case model of first recurrence to year 5

Modelled overall survival

As mentioned above the model made no distinction between treatment arms beyond states A, B and D. The difference in overall survival between treatments therefore rests on the difference between states A (no AT) and B + D (AT). This difference lies in the delay to recurrence experienced with adjuvant therapy, which after extrapolation of trial data approximates to 3 years or 3.5 years if the assumption of extended benefit is used. On this basis death in the adjuvant arm is delayed 3 to 3.5 years relative to the control arm and the overall survival curve is shifted by 3 (or 3.5) years. The difference in average survival (difference in areas under the curve) will then be 3 (or 3.5) years. Because the model considers states beyond A, B and D to be the same irrespective of treatment arm the difference in costs corresponds approximately to the cost of 3 years of adjuvant therapy = £58.59K (3 x 365

tablets at £53.47 each). Ignoring minor discounting differences from the 3 (or 3.5) year lag, we can expect an ICER of approximately £58.59K/3 = £19.5K /LYG (or £58.59/3.5 = £16.7/LYG). The manufacturer's base case ICER was £19.21K/LYG, which is very similar and tends to support to the simple estimate outlined above.

On this interpretation the model accepts the assumption that delay in recurrence translates directly into delay in death and improved survival. This is acknowledged on page 94 of the submission as follows *"the model assumes that benefits in terms of recurrence-free survival translate into benefits in terms of overall survival. In other words, following recurrence all patients experience the same length of time with metastatic disease until death".* Except in one sensitivity analysis (SA 15) the model has not been used to explore this assumption, and in fact in the form received by the ERG the model cannot be used for this purpose because all states beyond A, B and D have the same inputs for both treatments.

The model base case avoids any consideration of the possibility that adjuvant therapy for one or even for three years has an impact on resistance to subsequent imatinib treatment.

The base case model of overall survival was presented in Figures 19 and 22 of the submission (p89 and 94); the former figure is more difficult to interpret because the tick label is in multiples of eleven and the correspondence between label and tick is not obvious. Fig 22 is shown below but with 12 month gridlines added.

Confidential information removed

The ERG briefly investigated if the modelled survival for patients receiving adjuvant therapy merely represented a 3 or 3.5 year shift of the curve for those receiving surgery only. To do this the ERG fitted a Weibull distribution to the surgery only arm and generated adjuvant survival by displacing this curve by 3 and 3.5 years. The resulting overall survival curves are shown in Figure 8 superimposed on modelled curves from the submission. The fit to the surgery only curve is good and the 3 year shift in this curve corresponds closely to the manufacturers model of survival for patients receiving adjuvant imatinib.

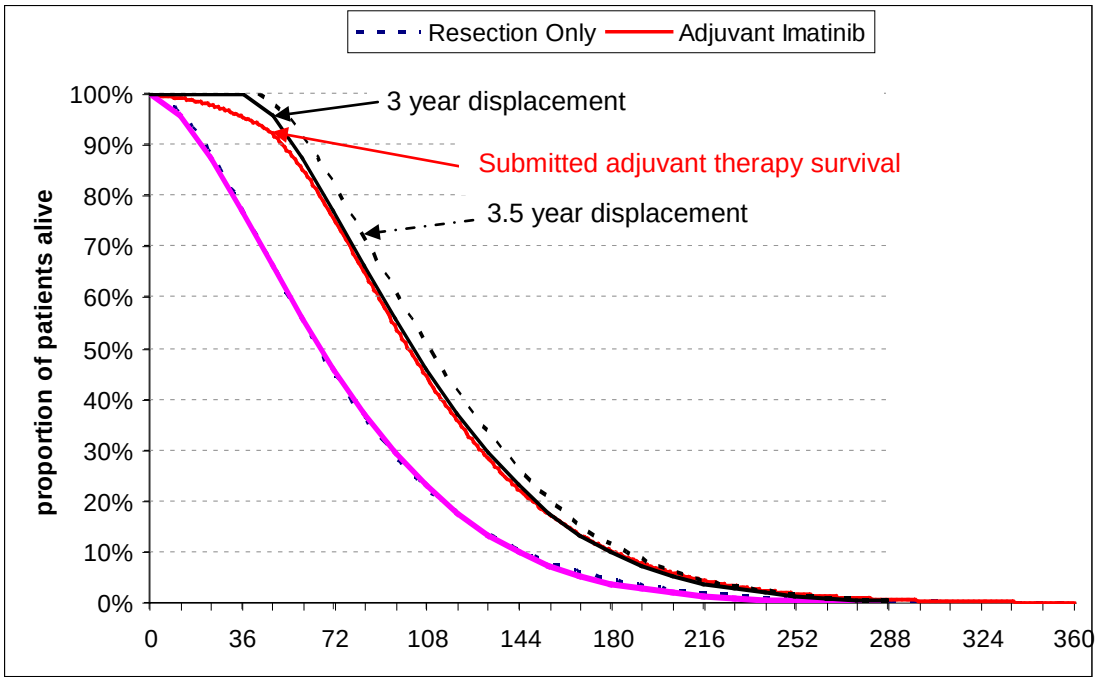


Figure 8 The survival for the adjuvant arm can be modelled by shifting the surgery only curve by 3 or 3.5 years

Sensitivity analyses based on MP of death

The manufacturer's original submission contained a sensitivity analysis (SA 15) that looked at the influence of the MP of death on the ICER. The MP of death in the recurrent state (stated to correspond to states C and F in the model) was changed so as to be greater in the adjuvant arm than the control arm; a factor of 4 was used, changing the MP death from 1.3% to 5.4% on 400 mg imatinib and 3.7% to 14.9% on 800mg imatinib). This reduced the life years gained from adjuvant therapy versus no adjuvant from 2.17 to 1.27 but only marginally altered the ICER which reduced from the base case of £22.94K/QALY to £20.31K/QALY. The ERG was unable to confirm this result because the model received did not have the facility for changing the MP of death independently in each arm. For such a large change in life years gained to have little effect on the ICER presumably results from considerable cost reductions in the adjuvant arm because fewer patients remain in imatinib treatment and fewer proceed to expensive sunitinib. An alternative sensitivity analysis would be to unilaterally reduce mortality in the surgery-only arm.

In response to request for clarification on the impact of MP of death on survival benefit of adjuvant therapy and resulting ICER the manufacturer undertook three further sensitivity analyses summarised below: From the clarification document:

(a) Changing monthly probability of death following GIST recurrence for first, second line treatment and BSC in both arms (applies for health states C, E, F, G and H on figure 13)
Increase by factor of 2 - £ 22 854
Increase by factor of 4 £22 887
Increase by factor of 6 - £ 22 914

(b) Changing probability of death following GIST recurrence of imatinib post recurrence first line treatment in both arms (applies for health states C and E on figure 13)
Increase by factor of 2 - £22 942
Increase by factor of 4 - £22 946
Increase by factor of 6 - £ 22 948

(c) Changing probability of death following GIST recurrence of imatinib post recurrence second line treatment in both arms (in health states F and G on figure 13)
Increase by factor of 2 - £22 960

All these sensitivity analyses link MP of death equally to both arms. A conclusion from the results is that when this is done changes to MP of death have essentially no effect on the resulting ICER. This supports the model interpretation outlined above.

In summary: by linking recurrence rates and mortality rates across both arms the model appears to be set up so that the delay in progression from adjuvant therapy translates *pro rata* into overall survival benefit.

5.1.5 Resources and costs

Cost data used in the evaluation were taken from a range of sources. Drug costs are provided by the manufacturer and are consistent with those found in the British National Formulary 58. All other costs are taken from standard sources in economic evaluations, including NHS references costs, Personal and Social Services Research Unit and estimates from local services. Although no estimates of uncertainty were provided for costs taken from the

Royal Hallamshire Hospital Trust, changes in the cost of these items are likely to have an insignificant impact on the results of the analysis.

Estimates of resource use were based on the trial data, relevant clinical guidelines and the literature. However, the manufacturer has not provided a breakdown of the expected resource use for an individual patient in their written submission. So for example the cost of a GP appointment is provided, but it is not clear how many GP appointments contribute to the monthly cycle cost. This data is available directly from the Excel model for the determined searcher, but is not reproduced in anything like that level of detail in the written report. Per cycle costs and resource use data as provided by the manufacturer are reproduced below.

Per cycle costs and resource use data as provided by the manufacturer is reproduced below.

Drug costs are given in Table 18, unit costs of care are given in Table 19 and costs by health state are given in Table 20 (pages 70 to 71 of submission).

Table 18 Drug Prices (Wholesale Acquisition Cost (WAC))

	Mean £	***Source/Comments***
Drug per day		
Imatinib 400mg	53.47	Monthly cost for imatinib is calculated by 365.25 days in each year x daily cost and divided by 12 months
Imatinib 800mg	106.94	
Sunitinib 50mg	112.10	Average monthly cost based on regimen of 4 weeks on, 2 weeks off treatment. The patient access scheme, in which the first treatment cycle of sunitinib is free to the NHS, is not taken into account in the base case. A reduction in the cost of sunitinib is explored in sensitivity analysis.

Table 19 Unit Costs of Care (non-inflated prices)

	Mean £	*SD* £	*Distribution*	*Source/Comments*
Treatment				
Complete blood count	5.50	-	Not used	Royal Hallamshire Hospital Trust 2007/8[61]
Liver function tests	12.00	-	Not used	Royal Hallamshire Hospital Trust 2007/8[61]
Routine OP visit	94	3.4		NHS reference cost 2006. 310M OP follow-up Medical Gastroenterology[62]
CT scan	147			2009/10 non-mandatory tariffs for unbundled diagnostic imaging for outpatients (including services accessed directly) Tariff RA13Z (chest/abdo/pelvis with contrast) [63]
Surgery (on recurrence)	3,656	111	Gamma	NHS reference costs 2005/6: : Average of HRG codes G02 Liver complex procedures (includes hemihepatectomy) G03 (Liver very major procedures (includes excision of lesion of liver) and F42 General abdominal - Very Major or major procedures (includes omentectomy) [61]
GP visit	30			Curtis 2007[64] Per surgery consultation of 11.7 minutes (with qualification costs, excluding direct care staff costs)

Table 20 Resource Utilisation by Health State (Monthly) - Average Medical Costs per Patient Including Gastroenterologist Visits, CT Scans, GP Visits (2009 Prices)

	Mean £	*SD* £	*Distribution*	*Source/Comments*
Recurrence-free GIST - no adjuvant therapy				
First 3 years	57	23	Gamma	assumptions on number of GP and GE visits and CT scans
4-5 years	47	24		
6+ years	39	22		
Recurrence-free GIST with adjuvant imatinib therapy				
First 3 months	206		Gamma	assumptions on number of GP and GE visits, blood & LFTs and CT scans
4 months - 2 years	46	33		
3 - 5 years	26	17		
6+ years	16	8		
Recurrence - Monthly medical costs - OP Visits, CT Scans, GP Visits (2009 Prices) (Note: this table excludes drug costs)				
Imatinib 400 mg/day	97	16	Gamma	assumptions on number of GP and GE visits and CT scans
Imatinib 800 mg/day	97	16		
Sunitinib second-line	97	15		

Table 20 Resource Utilisation by Health State (Monthly) - Average Medical Costs per Patient Including Gastroenterologist Visits, CT Scans, GP Visits (2009 Prices)		
Best Supportive Care (BSC)	548	7
Average cost of treating AEs	341	54
Recurrence – One off costs		
GP visits – one visit	34	
CT Scans – one scan	147	
GI Specialist OP - four visits	410	
Surgery (15% of recurrences)	548	
Total	**1 ,239**	

Note: this table excludes drug costs

At the clarification stage the ERG enquired why the total medical costs and the costs related to one-time recurrence were larger for “No treatment” than for “Adjuvant imatinib” (see Table 26, p95 of the submission and reproduced below). The manufacturer answered that these costs were average costs per patient over the lifetime horizon, not unit costs. This answer was unclear at best and misleading at worst. These costs are the average costs estimated in the economic model. How closely they reflect actual medical costs or recurrence costs that might be observed in clinical practice remains unknown as this data was not collected. Average patient cost from the economic model is influenced by a number of factors, but particularly the time-horizon and the choice of estimates for the probability of recurrence. Of greater benefit in the submission would have been a clear itemised breakdown of the monthly costs, including drug costs, for patients in each of the health states, as well as a separate reporting of the potential one-off costs to each health state every cycle of the model. Unit costs are partially reported in Tables 18 through 20 (see above) but not costs per cycle per health state. It is unclear which costs as reported in the above tables relate to which patients, in which state and at which time in the model.

From the submission, Table 26 (p95):

Table 26 Breakdown of Costs Per Patient

	Adjuvant Imatinib	No Treatment
Drug costs	£77,675	£35,858
Medical costs	£9,200	£9,289
One-time recurrence costs	£876	£1,002
AE costs	£114	£57
TOTAL COSTS	£87,865	£46,205

The costs and health outcomes (QALYs and LYs) associated with “No treatment” are the same whether the treatment duration is 3 years or 1 year. It is presumed, based on this fact that the results presented by the manufacturers in the results tables are from deterministic analysis. No probabilistic results are presented for analyses other than the base-case.

5.1.6 Discounting

The submitted excel model used appropriate discount rates for costs and benefits in line with NICE technical guidance. It appears that discount rates were appropriately applied in the model.

5.1.7 Sensitivity analyses

Whilst appropriate PSA was undertaken on the base case, it was not on the other scenario analyses due to the way the model is programmed. However, additional one way sensitivity analyses were conducted as part of the clarification process although no scenario analyses were undertaken on choice of model used to estimate long-term survival data.

As highlighted in section 5.1.3., no estimate of the uncertainty associated with the recurrence free state was included in the model. Given that all the estimates of utilities were taken from a literature review and not collected as part of the trial data a greater exploration of the uncertainty around health-related quality of life would have been beneficial.

We requested in the clarification document that the manufacturer provide a best and worst case scenario analysis. What the ERG expected to see were two scenarios – one where all values in the model were set to their least favourable for the experimental treatment and one where these values were set to the most favourable. However, in the clarification response the manufacturer simply highlighted the lowest and highest ICERs based on the analyses that had already been conducted. The difference between expectation and results may be related to ambiguity over the original phrasing of the request, however the manufacturers did request further clarity and it is the view of the ERG that what was expected was sufficiently clear and that the analyses should have been provided.

The economic analysis assumes that, after the treatment duration the recurrence rates in the imatinib arm revert to what is seen in the no-treatment arm, i.e. the rates in the imatinib arm for all years subsequent to the treatment period (plus six months) will come from patients who have not received adjuvant imatinib. The assumption that the treatment effect seen in the first year of the trial (the only year for which full data is available) will continue for the full three years is optimistic, considering there is no actual observed evidence for this. It is more likely that the probability of recurrence will increase over time even for those patients on adjuvant treatment. This would make imatinib treatment look less favourable compared with standard care. However, without credible alternative estimates, the ERG was not able to test these assumptions in the model provided.

The new base case PSA results showed a slightly higher mean ICER than that submitted previously. The manufacturer claims that in adapting the model to enable the PSA to be run for the one-year scenario, it was discovered that there was an error related to the year 4 recurrence rate for the three-year scenario. Therefore the correction explains changes in the results. We agree that this correction explains the changes in the mean ICER values, but it is the view of the ERG that this does not explain the large changes in the confidence intervals as there is much greater uncertainty in the revised

results. It is also the case that the changes they made were not explicitly presented to the ERG and so it is not possible to validate the results.

Sensitivity analysis around higher recurrence rates imatinib arm

The model base case assumes that benefits of a delay in recurrence translate directly into benefits in terms of overall survival over the long term (p94 of submission). The effect of resistance is not taken into account, however, we know that patients will eventually become resistant to imatinib over time (secondary resistance develops after a median of about two years of treatment[9]). This effect of earlier resistance in the adjuvant imatinib arm is explored in SAs 13 and 14 by increasing the recurrence rates in the adjuvant imatinib arm in year 2 and 3 by 10% (SA13) and 20% (SA14) respectively. These choices are arbitrary, as there is no evidence to support them. The effect of this is to marginally increase the ICER by £68 (SA13) and £136 (SA14). The fact that the ICER barely changes is probably due to the fact that earlier recurrence is linked directly to earlier death thus patients will have fewer life years, but also fewer expensive treatments. There is however no explanation given in the submission. This reasoning seems flawed to the ERG as there is no evidence of a delay in recurrence linked directly to an increase in survival. It is more likely that patients experiencing earlier recurrence will encounter more expensive treatment options earlier in the course of their disease (imatinib 800mg, sunitinib), without this necessarily having an effect on the mortality rate. Given the constraints of the model the ERG could not independently verify what effect changing the recurrence rates has elsewhere in the model. Using trial based recurrence rates (as in SA11) increases the ICER by a more substantial amount, approximately £6000. Again, an explanation of why there is a more substantial increase in this instance would have been helpful.

5.1.8 Model validation

The ERG did not identify any errors in the programming of the economic model provided; there were however concerns regarding input parameters to the model (see previous sections). It must be noted that the model was not amenable to changes in input values. The complexity of the model and the

lack of obvious user interface for most parameters is at the root of this difficulty. The ERG was not confident that making a change to a value in a given cell of the Excel file would be appropriately reflected throughout the model calculations. This limited the scope for the ERG to fully test and appraise the reliability of the model and the results presented by the manufacturer. This is also one reason why the ERG has been unable to conduct more than a limited range of alternative analyses using a range of values to test the assumptions made by the manufacturers (for example, on the utility value associated with being recurrence free). This reduces our confidence in the results of the economic model.

5.2 Critique of approach used

The model provided by the manufacturer contained no programming errors and the structure of the model reasonably reflected the natural history of the disease.

The utility values used in the submission rely heavily on a study by Chabot et al (ref 59 in the submission). Chabot et al highlight the sensitivity of their results to changes in utility estimates and advise caution in interpreting their results due to this uncertainty. In addition a number of flaws were identified in the modelling of health state utility. The manufacturers did not model utility values of less than zero arguing that the health state of progressive disease reflects an average of a cohort of patients. However, whilst use of the mean is valid in a deterministic context the range is needed for a probabilistic analysis. Additionally, the approach taken to calculate the age adjusted utility values assumes that patients who were recurrence free had otherwise perfect health. This is likely to underestimate utilities for patients in states other than no recurrence.

The ERG have some concerns regarding the monthly probabilities of death in various health states and their application in the model. The manufacturer provided no justification for the selection of studies from which the data is derived, no details on how the rates were calculated and there appeared to be some errors and inconsistencies. It is unclear how this uncertainty was accounted for in the model.

The manufacturer makes the basic assumption that a delay in recurrence translates directly into a survival benefit. As commented on elsewhere in the report, there is no evidence to underpin this assumption, furthermore the possibility of differing rates between the treatment arms of developing resistance to imatinib is not taken into account.

Cost data was taken from a range of appropriate sources with estimates of resource use based on the trial data, relevant clinical guidelines and literature. However, the manufacturer has not provided a breakdown of the expected resource use for an individual patient in the written submission. Unit costs are partially reported in Tables 18-20 but not costs per cycle per health state. No probabilistic results are presented for analyses other than the base-case.

As mentioned above, PSA was undertaken only on the base case. Whilst multiple one way sensitivity analyses were conducted, with additional analyses carried out as part of the clarification process there remains concern that more work could have been carried out to explore the uncertainty around the health related quality of life estimates (given these were taken from the literature) and best case and worst case scenario analysis.

The ERG was unable to test the assumption that the treatment effect seen in the first year will continue for three full years and considers this assumption optimistic.

The model assumes no estimate of uncertainty associated with the recurrence free health state. This is likely to have resulted in an overestimate of the benefit received by patients. This should have been included in the model as a component of the probabilistic analysis.

Finally, after clarification, the new base case PSA results showed a higher mean ICER than the previously submitted ICER following discovery of an error by the manufacturer. However, the revised results show greater uncertainty indicated by large changes in the confidence intervals and we are unable to validate the results presented.

5.3 Results included in manufacturer's submission

Results provided in the manufacturer's submission are presented below as they appear in the original submission or in the responses to the clarification questions. Included here are the base case results, results of the sub-group analyses and results of the one-way, scenario and probabilistic sensitivity analyses. Full comments on these results are presented in section 5.4 of this report. The manufacturer provided a revised estimate of the ICER alongside the revised economic model, dated the 22nd December, 2009. The revised estimates suggested a cost per QALY of £23,601, with an incremental cost of £41,625 and an incremental QALY gain of 1.95. The reason for this change when compared with the original submission was that they 'discovered that there was an error related to the year 4 recurrence rate for the three-year scenario' (Manufacturer Correspondence). What this error was or how it was changed was not explained. Total costs and QALYs resulting from the change were also not reported. It thus remains unclear what the direction or size of any effects of this change in parameter value had on the results of the model. Because of this uncertainty and the difficulty associated with validating the revised estimate, the results presented in the ERG report are based on the results from the original submission with the caveat that the revised ICER was marginally greater than the original estimate.

The manufacturer provided a full set of results using the base case assumptions and parameter inputs. In the base case, the population was defined as those at moderate or severe risk of recurrence (in line with the scope of the appraisal) following surgery who receive three years of imatinib. See Manufacturer's Table 25 on page 81 of this report for full base case results.

From page 93 of the manufacturers submission:

7.3.1 Base case analysis

7.3.1.1. What were the results of the base case analysis?

In the base case scenario, total costs are estimated to be £87,865 per patient in the imatinib arm and £46,205 per patient in the surgical resection only group. Total life-years and QALYs for patients treated with imatinib are estimated to be 7.75 and 5.89, respectively, and for the surgical resection only arm 5.58 and 4.08, respectively. This results in 2.17 life-years saved and 1.82 QALYs gained.

The manufacturer provided a full set of results for the following sub-group analyses that were conducted:

A) Significant risk patients, receiving imatinib for one year

B) The overall at-risk population (no treatment time specified)

C) The high-risk only population, receiving one year of imatinib

D) The high-risk only population, receiving three years of imatinib

These results are presented on page 81 of this report (Manufacturer's Table 27).

One-way sensitivity results for the base case and for a one year treatment period were presented as ICERs only; no details on the number of QALYs or costs associated with each strategy were presented. Full details, with each change made to the model, are presented on page 82 and 83 of this report in Manufacturer's Tables 28 and 29.

Cost-effectiveness acceptability curves and a cost-effectiveness scatter plot are provided by the manufacturer (Figures 23 and 24 of the original submission) for the base case analysis and are reproduced in this report on page 84. No CEACs or scatter plots were provided for any of the other scenarios tested, so it is not possible to assess the uncertainty in these results.

From page 93 of the manufacturers submission

Table 25 Total Costs, Outcomes and Incremental Cost-Effectiveness Ratios

	Total Per Patient			Incremental			ICERs	
	Costs	**QALYs**	**LY**	**Costs**	**QALYs**	**LY**	**Cost/QALY Gained**	**COST/LY Gained**
No Treatment	**£46,205**	**4.08**	**5.58**					
Adjuvant Imatinib	**£87,865**	**5.89**	**7.75**	**£41,590**	**1.82**	**2.17**	**£ 22,937**	**£ 19,210**

From page 95 of the manufacturers submission

Table 27 Total Costs, Outcomes and Incremental Cost-Effectiveness Ratios

	Total Per Patient			Incremental			ICERs	
	Costs	**QALYs**	**LY**	**Costs**	**QALYs**	**LY**	**Cost/QALY Gained**	**COST/LY Gained**
Base case: Significant risk population, 3 years' treatment duration							£ 22,937	£ 19,210
Scenario A: Significant risk population, 1 year's treatment duration								
No Treatment	£46,205	4.08	5.58					
Adjuvant imatinib	£60,804	5.02	6.69	£14,599	0.939	1.11665	£15,550	£13,074
Scenario B: Overall population								
No Treatment	£32,757	7.56	9.84					
Adjuvant imatinib	£73,737	8.80	11.35	£40,979	1.24	1.15	£32, 981	£27,276
Scenario C: Sub-group analysis, high risk only – 1 year's treatment duration								
No treatment	£43,589	4.62	6.25					
Adjuvant imatinib	£54,946	6.47	8.49	£11,356	1.86	2.23	£6,109	£5,084
Scenario D: Sub-group analysis, high risk only – 3 years' treatment duration								
No treatment	£43,589	4,62	6,25					
Adjuvant imatinib	£84,072	6,66	8,70	£40,483	2,043	2,45	£19,813	£16,527

For scenario B, the ICER is somewhat higher than the base case. This is to be expected, given that this scenario includes patients who are expected to receive no benefit from adjuvant treatment.

From page 96 of the manufacturer's submission.

Table 28 Sensitivity Analysis Results – Base case

	UK Inputs	ICER
Base Case		**22,937**
SA 1	As base case with cost of AEs doubled	22,968
SA 2	As base case + dose intensity reduction	22,148
SA 3	As base case with alternative cost for BSC	
	+20%	22,854
	-20%	23,019
SA 4	As base case + surgery costs	
	doubled	22,903
	halved	22,953
SA 5	As base case but with sunitinib cost reduced by 20%	22962
SA 6	Utility : Without age adjustment for utility	18,514
SA 7	Utility : Utility of BSC lowered by -0.2 to 0.37	22,683
SA 8	Utility : Recurrence free patients' utility set to 0.95	24,300
SA 9	Utility : 0.081 utility decrements associated with adjuvant imatinib treatment for 3 years	25,623
SA 10	Utility : 0.081 utility decrements associated with adjuvant imatinib treatment for first year only	23,846
SA 11	Alternative recurrence rates assumption (trial based)	28,851
SA 12	Recurrence rates for placebo declining over time (historical trend)	21,620
SA 13	Recurrence rates of adjuvant imatinib increased in year 2 and 3 by 10%	23,005
SA 14	Recurrence rates for adjuvant imatinib increased in year 2 and 3 by 20%	23,073
SA 15	As base case + reduced survival on imatinib in metastatic setting (mortality rate increased by factor of 4)	20,310
SA 16	Time horizon – 5 years Sensitivity Analysis Results – Base case	40,159

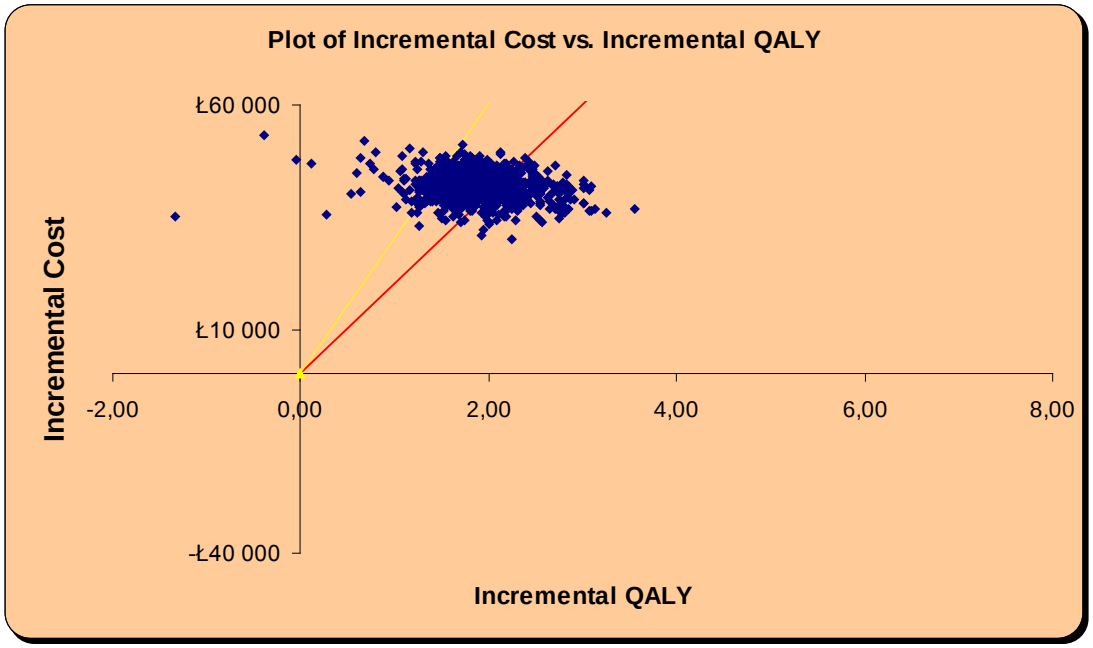
From page 98 of the manufacturer's submission.

Table 29: Sensitivity Analysis Results: One year treatment scenario

	UK Inputs	ICER
	Base Case	**15,550**
SA 1	As base case with cost of AE doubled	15,614
SA 2	As base case + dose intensity reduction applied	15,008
SA 3	As base case + BSC	
	+20%	15,469
	-20%	15,630
SA 4	As base case + surgery costs	
	doubled	15,518
	halved	15,566
SA 5	As base case with price of sunitinib reduced by 20%	15,576
SA 6	As base case + without age adjustment for utility	12,610
SA 7	Utility of BSC lowered by -0.2 to 0.37	15,381
SA 8	As base case + recurrence free patients' utility set to 0.95	16,472
SA 9	As base case + 0.081 utility decrements associated with adjuvant imatinib treatment for 3 years	Not applicable
SA 10	As base case + 0.081 utility decrements associated with adjuvant imatinib treatment for first year only	16,789
SA 11	Alternative recurrence rates assumption (trial based)	27,897
SA 12	Recurrence rates for placebo declining over time (historical trend)	8,856
SA 13	Recurrence rates of adjuvant imatinib increased in year 2 and 3 by 10%	Not applicable
SA 14	Recurrence rates for adjuvant imatinib increased in year 2 and 3 by 20%	Not applicable
SA 15	As base case + reduced survival on imatinib in metastatic setting (mortality rate increased by factor of 2)	9,997
SA 16	Time horizon – 5 years	18,203

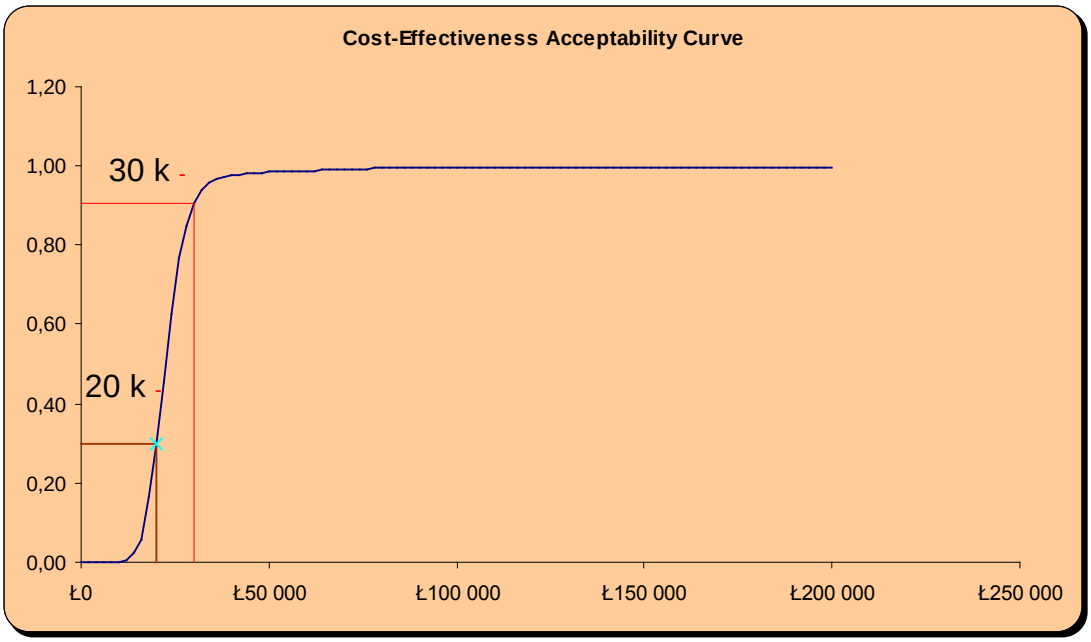
From page 97 of the manufacturer's submission.

Manufacturer's Figure 23: Scatter plot of incremental cost and incremental QALY – base case



From page 98 of the manufacturer's submission

Manufacturer's Figure 24: Cost effectiveness acceptability curve – base case



5.4 Comment on validity of results presented with reference to methodology used

The ERG have serious concerns about the validity of the results presented by the manufacturers. These are centred primarily on the approach used to estimate health related quality of life, the reporting of costs in the economic model and in the estimation of survival following resection. The details of each point are discussed in sections 5.1.1 through 5.1.7. In this section we present a summary of these points with respect to the validity of the model. In section 5.5 we discuss these points in relation to the uncertainty that arises as a result.

It is not clear from the original submission or from the responses to clarification questions whether or not the utility values used in the model are a true reflection of the value patients treated with imatinib would place on their own health states. When uncertainty exists around health related quality of life to the degree shown in this report the results must be treated as highly uncertain.

In addition to the choice of the utility estimates, there are concerns over the way these estimates have been applied in the model. A patient in any given health state has had an adjustment applied to their utility value according to an age-adjusted utility values estimated for the general population. This will lead to a double counting of the decrement in utility experienced by a patient. First, they have had a utility loss estimated as a result of their current health state. And then this has utility loss has been made larger by the assumption that because of the age of the patient they must be in a worse health state than they have claimed to be in themselves. This clearly leads to a potential for double counting and given that this will affect patients in the worst health states the greatest, the likely effect is to favour the manufacturer’s treatment.

Health related quality of life is a key driver of the cost-effectiveness of imatinib. Small changes to the number of QALYs that are estimated to be

gained from treatment can lead to large changes in the incremental cost-effectiveness ratios. If the way in which QALYs are estimated in any economic model is not reliable than the results are unlikely to be valid. Therefore the conclusion that must be drawn is that the numerous problems that we have identified in the choice of utility values and their application in the model is that there are significant doubts about the validity of model.

The reporting of costs in the manufacturers submission was poor. Only on close inspection of the model could the full details of the total and unit costs of treatment be ascertained. However, the costs in the model were appropriate and applied in a methodologically sound fashion. It is therefore only the reporting of costs, rather than they were used in the model that may lead to uncertainty in the interpretation of the results.

There is a lack of detail provided by the manufacturer on how estimates of monthly probabilities of death were derived, and the way they were applied in the model. The ERG has concerns around the fact that the same probabilities of death were applied to different health states regardless of how they were arrived at (i.e. after adjuvant imatinib or placebo). The model did not allow for separate inputs to health states according to treatment arm.

A transition matrix identifying the probability of moving between states at the end of any given cycle was requested in the clarification stage but was not provided by the manufacturer. This adds to the difficulties in assessing the validity of the model. This also means that it is not possible to address the lack of clarity around the ways in which recurrence free survival estimates were calculated.

The assumptions around the monthly probability of recurrence on adjuvant treatment are quite probably optimistic and favour the manufacturer. There is no observed evidence to suggest that recurrence rates stay constant over the three modelled years. This is particularly significant when the trial data is only available for one year in this population. More credible estimates might suggest that rather than a step change between years three and four as currently modelled, there would be a gradual change from year one to three,

followed by an increase in the rate between years three and four. This would likely make the ICER estimate for the base case less favourable to adjuvant therapy. However, as noted elsewhere in this report, the executable model provided by the manufacturer was not user friendly and such changes in the estimates could not be reliably tested.

5.5 Summary of uncertainties and issues

The economic model submitted by the manufacturer for this appraisal contained no errors in the programming, however there were concerns regarding the validity of some inputs and the model was not amenable to changes in input values. The ERG was not confident that making a change to a value in a given cell of the Excel file would be appropriately reflected throughout the model calculations. This is one reason why the ERG has been unable to conduct more than a limited range of alternative analyses using a range of values to test the assumptions made by the manufacturers.

Issues of uncertainty include those related to utilities, which, in part, emanate from use of utilities taken from the literature. For example, the uncertainty associated with the recurrence free state; but also result from flaws in the modelling of health state utility. These issues mean that not only is the accuracy of the estimated benefit of the treatment in terms of QALYs called to question but that, the model does not allow us to even estimate in which direction these are likely to be wrong.

Whilst appropriate PSA was undertaken on the base case, it was not on the other scenario analyses due to the way the model is programmed. In particular PSA was not undertaken in the sub-group analysis. Whilst one way sensitivity analyses were conducted as part of the clarification process no scenario analyses were undertaken on choice of model used to estimate long-term survival data.

Following the manufacturer’s changes to the ERG responses the new base case PSA results showed a slightly higher mean ICER than that submitted previously but with much greater uncertainty in the revised results. The manufacturer claims that in adapting the model to enable the PSA to be run

for the one-year scenario, it was discovered that there was an error related to the year 4 recurrence rate for the three-year scenario. Therefore the correction explains changes in the results. We agree that this correction explains the changes in the mean ICER values, but it is the view of the ERG that this does not explain the large changes in the confidence intervals. It is also the case that the changes that they made were not explicitly presented to the ERG and so it is not possible to validate the results presented.

The basic assumption made by the manufacturer that a delay in recurrence translates directly (*pro rata*) into a survival benefit is not supported by any evidence, and does not take into account potential differences in the treatment arms in the development of resistance to imatinib.

6 Additional work undertaken by the ERG

Additional searches to confirm completeness of published data on effectiveness and cost-effectiveness were undertaken.

As identified throughout the ERG report and indicated by the manufacturers in their response to clarification questions, the executable model was not amenable to changes in parameter values, particularly with reference to running alternative probabilistic analyses. Other problems with running additional analyses include the lack of information around uncertainty estimates for certain parameters, particularly the utility value associated with the recurrence free health state. We present results for variation in this value below. What can be seen is that although the ICER increases as the estimate of the utility value decreases, these changes are relatively small. Earlier caveats about the difficulty in confirming the validity of results due to the opaque nature of the model should still be born in mind when considering these results.

Despite the uncertainty in the parameter values and uncertainty estimates for the recurrence free survival used in the model the ERG are unable to conduct analyses based on alternative estimates for recurrence free survival. There is insufficient data available to the ERG in the submission to select credible alternative survival estimates and it is beyond the scope of the STA process

and timelines for the ERG to undertake its own systematic review of this evidence.

Sensitivity analysis where recurrence free survival utility value is set equal to 0.95 (deterministic results only):

Cost-effectiveness results for adjuvant imatinib compared to no treatment

	Total Per Patient:			Incremental:			ICERs	
	Costs	QALYs	Life-Years	Costs	QALYs	Life-Years	Cost/QALY Gained	Cost/LY Saved
No treatment	£46,205	3.95	5.58					
Adjuvant imatinib	£87,865	5.66	7.75	£41,659	1.714	2.16860	**£24,300**	**£19,210**

Sensitivity analysis where recurrence free survival utility value is set equal to 0.90 (deterministic results only):

Cost-effectiveness results for adjuvant imatinib compared to no treatment

	Total Per Patient:			Incremental:			ICERs	
	Costs	QALYs	Life-Years	Costs	QALYs	Life-Years	Cost/QALY Gained	Cost/LY Saved
No treatment	£46,205	3.82	5.58					
Adjuvant imatinib	£87,865	5.43	7.75	£41,659	1.613	2.16860	**£25,835**	**£19,210**

7 Discussion

7.1 Summary of clinical effectiveness issues

Main results

• Adjuvant imatinib given for one year delays recurrence in a KIT positive population with significant risk of recurrence; the one year RFS rate was 98.3% (adjuvant imatinib) versus 71.5% (placebo).This is based on a median observation time of [redacted]

[redacted]

[redacted]

• There is little data on the development of resistance to imatinib over time with different treatment strategies; some data suggest similar response rates with repeated use but this is based on small patient numbers and is short-term.

Comments by the ERG

There are some uncertainties associated with the effect estimates. The significant risk group is a sub-group of the original trial population, and, as risk levels could only be assigned retrospectively to 78% of randomised patients, this may result in differences in patient characteristics between the treatment and placebo arms (selection bias). The significant risk Z9001 trial population is likely to be similar to a UK population that would be eligible for adjuvant GIST, although using different classification methods may result in slightly different thresholds for ‘significant’ risk. The Z9001 trial excluded patients who have previously had imatinib for advanced disease and then became eligible for resection. These patients would potentially be eligible for adjuvant imatinib in the UK. This is likely to be a small patient group and patients are unlikely to

be comparable to those receiving adjuvant imatinib for the first time after resection.

There are no details in the submission on how missing data was handled or the effect of sensitivity analyses around this. There are also no details on which definition of recurrence was used and the effect of using alternative definitions.

Nevertheless, there is evidence of a delay in recurrence, although we cannot be certain of the exact effect size. The median follow-up times are short ([redacted] recurrence free survival and [redacted] overall survival), so the data is still immature. The planned follow-up time is five years. Therefore we have little indication of the longer-term effects of one- year adjuvant imatinib.

There is no evidence on the effect of giving adjuvant imatinib for three years in the submission, however, this is what the base case in the economic model assumes. Alternative data sources have been used for these assumptions.

Since all patients are eligible to receive imatinib, whether as adjuvant therapy or, if applicable, on recurrence, the question of interest is not whether patients survive longer with adjuvant imatinib or placebo, but whether giving imatinib earlier (adjuvantly, at a disease free stage) rather than later (once disease has recurred) confers a survival benefit. This has not (yet) been shown by any trials.

This issue is addressed by Hohenberger (2009)[25] who points out that there is a problem of proving the value of adjuvant imatinib in increasing survival in the presence of highly effective palliative treatment. We also don’t know whether adjuvant imatinib prevents or delays recurrence, whether adjuvant imatinib will affect the response to imatinib reintroduction in the metastatic phase, or the optimal duration of treatment.

Gronchi et al. (2009)[14] argue that, after completion of the Z9001 trial, we are currently faced with two scenarios:

"(1) wait 6-7 years for the results of overall survival, but until then deny our patients the opportunity to receive a possibly life-improving treatment? Or

(2) conversely, offer imatinib to all patients thus exposing them to a treatment which delays relapses but whose consequences on secondary resistance are not yet known."

A decision has been made within the Intergroup GEIS/EORTEC/ISG/FSG/ AGITG 62024 trial to explore time to imatinib resistance as a possible surrogate endpoint.[14] One study found that secondary resistance develops after a median of about two years of imatinib treatment.[9]

We have little data on long-term development of imatinib resistance with the two treatment strategies. In the Z9001 trial, 23 patients who relapsed after their 12 month treatment had been completed were offered repeat imatinib; [redacted]. This is based on very small patient numbers and associated with considerable uncertainty. The submission states that in seven of these duration of response was in excess of 19 months and that in most patients treatment was ongoing. Detailed outcome data was not provided for all patients. We do not know what will happen in the longer term to these patients. The study by Blay (2007) also looks at imatinib resistance after continuous use and interrupted use (albeit in a population with advanced GIST, so not in an adjuvant setting). The study found little difference in resistance between the two treatment arms, however there are a number of uncertainties: we do not know the mean treatment gap in the INT arm or the median follow-up time, and the study is based on small patient numbers. There is no evidence of a difference in overall survival.

There is a lack of evidence regarding the total length of time a patient will derive benefit from imatinib and whether this will vary depending on whether they receive it adjuvantly (for one or three years), continuously or with treatment gaps, or on recurrence only. There is also no clear evidence on whether the delay in recurrence is affected by the length of time the adjuvant therapy is given.

Regarding overall survival, the submission uses the analogy of adjuvant treatment of breast cancer, which our clinical expert suggests is inappropriate for GIST. We know that chemotherapy can eradicate micrometastases in breast and bowel cancer and hence prevent recurrence and the use of recurrence free survival as an early surrogate for overall survival has been validated. However, imatinib has a very different mode of action and we don't know if early treatment will eradicate metastases and prevent recurrence or whether it will simply delay recurrence.

Some may take the view that prolonging recurrence free survival is in itself a worthy treatment goal, regardless of the effect on overall survival. We have no evidence that adjuvant imatinib will have a detrimental effect on survival, so it could be argued that, at worst, survival will be the same (+/- adjuvant imatinib), but progression will be delayed. However, adjuvant treatment may be less well tolerated by patients than treatment for active disease; this is because patients feel well in terms of the disease but can experience side effects from the adjuvant treatment. In patients who are feeling unwell from the disease, the benefit from the treatment in terms of alleviating disease symptoms may outweigh potential side effects. We have identified no quality of life data (for patients with disease, after resection or on adjuvant imatinib), which would help to inform this question. Given the lack of clear evidence on potential benefit or harm, and setting aside cost considerations, it is likely that any clinical decision to give adjuvant imatinib would need to consider patient preference to a large extent.

We know that some patients will be cured by surgery and will never need imatinib. So those patients who continue to be recurrence free on long-term imatinib may be those patients who didn't need imatinib in the first place. This is less likely to be the case where only high risk patients are treated adjuvantly.

Adjuvant imatinib is licensed in the UK for the treatment of KIT positive adult patients who are at significant risk of relapse following resection. However, there may be sub-groups of patients who are likely to benefit more or less from adjuvant imatinib. Mutational analysis is likely to be relevant on an

individual patient basis with some research suggesting that certain mutations are likely to be more or less sensitive to imatinib in an adjuvant setting.

7.2 Summary of cost effectiveness issues

The model submitted by the manufacturer is complex and not readily amenable to changes in input values. The complexity of the model and the lack of obvious user interface for most parameters meant that the ERG was not confident that making a change to a value in a given cell of the Excel file would be appropriately reflected throughout the model calculations. This limited the scope for the ERG to fully validate the model and to undertake alternative analyses, and thus reduced the ERGs confidence in the results of the model.

The ERG has concerns about a number of aspects of the submitted analysis: It is likely that the approach to the modelling of the utility data for the cost effectiveness analysis systematically favours imatinib and thereby incorrectly reduces the incremental cost effectiveness ratio.

The assumption of sustained benefit from treatment for two years beyond the evidence base is a generous one and also systematically favours imatinib and again reduces the estimated incremental cost effectiveness ratio.

The use of a lifetime cost in the model may inappropriately narrow the gap in costs between the imatinib and no treatment group. However insufficient data has been provided to establish the direction of effect.

The absence of probabilistic sensitivity analysis for the sub-group analyses provided further exacerbates the paucity of the evidence on the uncertainty around the cost effectiveness estimates provided in the submission.

The lack of sensitivity analysis on alternative models of recurrence free survival is a potentially important omission as survival is a major driver of the benefit from treatment and it is likely that the results are highly sensitive to changes in the parameter.

The manufacturer's choice of survival parameters was not explained, was applied inconsistently and appeared to be arbitrary. As stated earlier, the ERG believes the basic assumption made by the manufacturer that a delay in recurrence translates directly (*pro rata*) into a survival benefit is not supported by any evidence, and does not take into account potential differences in the treatment arms in the development of resistance to imatinib.

Whilst it is credible that the direction of effect of the majority of these problems is to inappropriately reduce the estimated Incremental Cost Effectiveness Ratio, the complexity and opaqueness of the submitted model made it effectively impossible for the ERG to undertake the desirable alternative analyses to quantify the impact. Therefore, the ERG can only advise that the submitted estimates be treated with considerable caution.

7.3 Implications for research

Further data on recurrence free survival and overall survival may be provided by longer-term follow-up of the Z9001 trial. The ongoing EORTEC 62024 trial compares two years of adjuvant imatinib to placebo and the SSG XVIII/A1 trial compares one to three years of adjuvant imatinib, so results from these trials may provide information on optimum treatment lengths. However, there are no interim results available yet and it is likely that it will take several years for useful data on overall survival to become available. Finally, further research is required to identify the type of patient, based on mutational analysis and other risk factors, most likely to benefit from adjuvant treatment.

Appendix 1 List of those involved with developing the ERG scope.

Please refer to NICE.

Appendix 2: Quality assessment using ScHARR-TAG economic modelling checklist

Title

Imatinib as adjuvant treatment for adult patients who are at significant risk of relapse following resection of KIT positive gastrointestinal stromal tumours

A statement of the problem

A statement of the problem is included in the submission and reflects the decision problem as set out in the scope.

A discussion of the need for modelling

Included; the manufacturer states ‘A Markov modelling technique was used in order to capture the ongoing risk of recurrence over time’.

A description of the relevant factors and outcomes

Yes, a description was provided in both the submission and clarification document.

A description of model including: type of model; time frame; perspective; and setting

A description was provided. A lifetime Markov model was used. The model is run over a 50 year time horizon. All patients begin the model free from recurrent GIST either receiving no treatment following surgical resection or receiving imatinib as adjuvant therapy. Each model cycle lasts for one month. Patients are followed until death.

A description of data sources, with description of respective strengths and weaknesses

The utility values used in the submission rely primarily on one previous study whilst cost data were taken from a range of sources. More detail should have been provided.

Key assumptions relating to model structure and data stated

Yes, key assumptions relating to the model structure were included in both the submission and clarification documents.

Disease specific factors included within modelling (Items to be specified in conjunction with expert clinical input)

Yes, included within the modelling.

Validation

Model validation was difficult, as the executable file was not designed for changes to be made by users of the model. The model runs as specified and generates the results as presented in the written submission for those scenarios that can be altered by the user.

Results

Results are provided in the submission and are consistent with those obtained from the executable model.

Sensitivity analysis results

One-way and scenario analyses were conducted and reported. Probabilistic sensitivity analysis was undertaken for the base-case scenario with CE scatter plots and CEACs reported.

Appendix 3: The NIH or Fletcher 2002[4] scheme

Proposed Approach for Defining Risk of Aggressive Behavior in GISTs

	Size*	Mitotic Count†
Very low risk	<2cm	<5/50 HPF
Low risk	2-5cm	
Intermediate risk	<5cm 5-10cm	6–10/50 HPF <5/50 HPF
High risk	>5 >10 Any size	<5/50 HPF Any mitotic rate >10/50 HPF

Abbreviation: HPF, high-power field.

*Size represents the single largest dimension. Admittedly this may vary somewhat between prefixation and postfixation and between observers. There is a general but poorly defined sense that perhaps the size threshold for aggressive behavior should be 1 to 2 cm less in the small bowel than elsewhere.

†Ideally, mitotic count should be standardized according to surface area examined (based on size of high-power fields), but there are no agreed-on definitions in this regard. Despite inevitable subjectivity in recognition of mitoses and variability in the area of high power fields, such mitotic counts still prove useful.

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