NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Imatinib for the adjuvant treatment of gastrointestinal stromal tumours (review of TA196)

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Key issues for consideration

Clinical effectiveness

- The manufacturer noted that the baseline characteristics in ACOSOG Z9001 and the SSGXVIII/AIO study were balanced across treatment groups. The ERG stated that differences were more pronounced in the high-risk subgroups, indicating selection bias. What is the Committee's view on the robustness of the clinical-effectiveness results from the high-risk subgroups?
- ACOSOG Z9001 was unblinded after the primary analysis and patients randomised to placebo who had not experienced disease recurrence were allowed to cross over to treatment with imatinib for 1 year, which confounded the results of the 5-year follow-up analysis. The manufacturer presented analyses where patients were censored at the time of crossover, and these hazard ratios were lower than the intention-to-treat analysis. The manufacturer presented several methods of adjusting for crossover including censoring (per-protocol analyses at the time of switching or excluding patients who crossed over) and statistical methods (rank preserving structural failure time model, the iterative parameter estimation algorithm and the inverse probability of censoring weights ([IPCW]). The preferred approach in the report provided by the manufacturer was the IPCW method, and the ERG agreed that this was appropriate. Does the

Committee consider that the impact of crossover has been incorporated appropriately?

Cost effectiveness

- Imatinib's European marketing authorisation for the adjuvant treatment of GIST covers adult patients who are at 'significant' risk of relapse following after surgery. Does the Committee consider it appropriate to appraise imatinib as an adjuvant treatment for a patient group at high risk of recurrence, and exclude patients at medium risk of recurrence in the absence of sufficient evidence?
- To estimate the risk of recurrence for patients treated with surgical resection followed by 1 and 3 years of adjuvant imatinib, the manufacturer applied the estimated treatment effect for imatinib (during and after stopping treatment) to the baseline risk of recurrence for patients treated with surgical resection only. The ERG noted that the manufacturer's overall approach required considerable post-hoc re-organisation of the trial data and stated that it may be more appropriate to use the crossover-adjusted recurrence-free survival estimates to derive clinical effectiveness parameters from ACOSOG Z9001.Does the Committee agree?
- The manufacturer's model defined the health states based on treatment, rather than explicitly modelling disease progression. The ERG stated that some of the later progressions in the model did not seem to be appropriate. For example, patients who had discontinued treatment because of adverse events then received best supportive care even though they had not experienced disease recurrence. Does the Committee find the transitions between the different health states to be acceptable?
- The manufacturer modelled baseline risk of progression using primary analysis data for patients in the placebo arm of ACOSOG Z9001 who had been identified as being at high risk of recurrence in the 5-year follow up analysis (n=98). The ERG noted that only data for these patients prior to unblinding (that is, before they were eligible to cross-over) were used, and that the manufacturer's submission does not state clearly the maximum follow-up for placebo patients before censoring. Is the Committee satisfied with the methodology used for modelling the baseline risk of recurrence, including the handling of crossover?

- The manufacturer estimated the on-treatment recurrence-free hazard ratio for the high-risk population using a direct comparison between the placebo and 1-year adjuvant imatinib arms in ACOSOG Z9001, using the Cox proportional hazards model with the data truncated at 12 months, giving a value of 0.111 (95% CI, 0.043 to 0.281). The ERG requested clarification regarding this hazard ratio, which is lower than the hazard ratio of 0.265 (95% CI 0.148 to 0.477) that was reported in the clinical-effectiveness section of the manufacturer's submission, but is still unclear after receiving the manufacturer's response. Does the Committee find the on-treatment hazard ratio used in the manufacturer's model to be acceptable?
- The ERG was concerned that on-treatment and off-treatment hazard ratios seemed to be derived using semi-parametric Cox proportional hazards models, which were then applied to the baseline risk (that is, with surgery alone) that was derived using fully parametric survival functions. It was unclear why the manufacturer had not used hazard ratios derived using the same parametric survival functions as those used in the model. Does the Committee consider the inconsistency in the manufacturer's methods for estimating recurrence-free survival for the different treatment types to be acceptable?
- The ERG noted that the long-term survival extrapolations varied substantially for different parametric functions and judgements between functions were primarily made on the basis of the validity of these extrapolations for recurrence-free survival at 5 years. The ERG stated that the manufacturer had adequately justified the rejection of the exponential, Weibull and gamma models but was unclear why the Gompertz model was chosen for the base-case analysis rather than the loglogistic model. The ERG was concerned that extrapolations based on the Gompertz function suggested a long-term maintenance of recurrence-free survival in around 30% of patients who received 3 years' adjuvant imatinib treatment. Does the Committee consider the choice of the Gompertz model to be appropriate and adequately justified?
- The ERG was uncertain about the appropriateness of some of the utility values used by the manufacturer because of a lack of detail in the manufacturer's evidence submission. Is the Committee satisfied with the utility values used in the manufacturer's economic model?

- The manufacturer's model assumed that 3.48 cycles of sunitinib were provided whereas the ERG estimated an average of 2.89 cycles (based on a median of 2 cycles reported in clinical trials). Using the lower number of cycles reduced the estimated monthly cost of sunitinib from £1615 to £1231 (including the patient access scheme). Is the Committee satisfied with the manufacturer's approach to incorporating costs for sunitinib?
- Does the Committee consider adjuvant imatinib for GIST to be an innovative treatment?

1 Background: clinical need and practice

1.1 Gastrointestinal stromal tumours (GISTs) are rare connective tissue tumours. Although GISTs can occur along the length of the GI tract, the majority arise in the stomach (60–70%) or small intestine (25–35%). GISTs are associated with the overexpression of several tyrosine kinase growth receptors and the ligands that bind to them. Around 75–80% of GISTs have activating mutations in c-KIT (CD117), a tyrosine kinase receptor, and 5–10% in platelet-derived growth factor receptor-alpha. These factors are thought to be important in driving tumour development and some specific mutation types can help in predicting clinical response to treatment.

1.2 The annual incidence of GIST is estimated to be approximately 900 new diagnoses per year in the UK and approximately half of these are likely to be resectable. Although GISTs can occur at any age, mean age at presentation is 50–70 years and it is more common in men than women.

1.3 Complete surgical excision is the current standard treatment for localised GISTs. NICE technology appraisal guidance 196 does not recommend imatinib for the adjuvant treatment of GISTs after surgery, and watchful waiting is the current standard of care. Risk stratification schemes have been developed to predict the likelihood of GIST recurrence. Current UK clinical guidelines recommend that at diagnosis, all patients with c-KIT (CD117)-positive GIST should be stratified as being at very low, low,

moderate or high risk of recurrence according to Miettinen 2006 criteria, which take into account tumour size, mitotic count and tumour location. An alternative risk classification scheme is the US NIH Consensus Criteria (2002), which is based on tumour size and tumour mitotic count. Recurrence occurs in 40–50% of patients who have had complete resection and the survival rates after complete resection are 88% at 1 year and 54% at 5 years.

2 The technology

2.1 Imatinib (Glivec, Novartis Pharmaceuticals) is a selective kinase inhibitor. Imatinib binds to activated c-KIT receptors and blocks the cell signalling pathway, preventing uncontrolled cell proliferation. Imatinib is administered orally. Imatinib has a UK marketing authorisation for the 'adjuvant treatment of adult patients who are at significant risk of relapse following resection of KIT (CD117)-positive GISTs. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment'.

2.2 The summary of product characteristics lists the following adverse reactions for imatinib: gastrointestinal effects, oedema, rash and neutropenia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The summary of product characteristics recommends a dose of 400 mg/day of imatinib for the adjuvant treatment of adults following resection of GISTs. Imatinib is available in doses of 100 mg (60-tab pack) and 400 mg (30-tab pack) at net prices per pack of £862.19 and £1724.39 respectively (excluding VAT; 'British national formulary' [BNF] edition 67). At a dose of 400 mg/day, drug costs for a course of treatment would be approximately £20,700 for 1 year and £62,100 for 3 years. The net price of imatinib has risen since the original appraisal of imatinib for the adjuvant treatment of gastrointestinal stromal tumours (NICE technology appraisal guidance 196). At that time, drug costs for a 1-year course of treatment (400 mg/day) would have been approximately £19,500. Costs

may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of imatinib within its licensed indication for the adjuvant treatment of gastrointestinal stromal tumours.

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Adults who are at significant risk of relapse following resection of KIT (CD117)-positive GIST	Adults who are at high risk of relapse following resection of c-KIT (CD117)-positive GIST

The manufacturer highlighted that 'significant' was not defined in the marketing authorisation, but had been interpreted to mean moderate and high risk of relapse. The manufacturer advised that the population presented in its submission was a subgroup of patients at high risk of disease recurrence, based on a retrospective analysis of patient baseline risk according to the Miettinen 2006 criteria. It explained that it had excluded patients at moderate risk of relapse because evidence was limited, and that it was unlikely that adjuvant imatinib would be used to treat these patients in UK clinical practice. The ERG considered omitting patients with moderate risk to be a limitation, but also noted that there was only limited randomised controlled trial evidence for this population.

	Final scope issued by NICE	Decision problem addressed in the submission
Intervention	Imatinib as an adjuvant therapy after surgery	Imatinib as an adjuvant therapy after surgery
Comparators	Observation after surgery (no adjuvant therapy)	Observation after surgery (no adjuvant therapy) via indirect comparison for 3 years' duration

Outcomes	The outcome measures to be considered include: • overall survival • recurrence-free survival • adverse effects of treatment • health-related quality of life.	The outcome measures to be considered include: • overall survival • recurrence-free survival • adverse effects of treatment • health-related quality of life
Economic evaluation	Cost effectiveness should be expressed as incremental cost per quality-adjusted life year. The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between technologies. Costs will be considered from an NHS and Personal Social Services perspective. Where appropriate, costs of any additional biomarker testing should be considered.	Cost-effectiveness will be expressed in terms of incremental cost per quality-adjusted life year. A lifetime time horizon has been chosen to capture all relevant outcomes and costs over the lifetime of patients with GIST. Recurrent disease may lead to death from GIST and patients who receive adjuvant treatment have a reduced probability of recurrence. Therefore, this potential survival benefit is accrued over the remaining patient lifetime. Costs have been considered from an NHS and Personal Social Services perspective.
Other considerations	If evidence allows, subgroup analyses by baseline risk of relapse and tumour genetic mutational status should be considered. Consideration should be given to number of treatment cycles and continuation rules for treatment if clinically appropriate. Guidance will only be issued in accordance with the marketing authorisation.	Subgroup analysis presented for patients classified at high risk of relapse according to the Miettinen criteria Economic evaluation assumed that adjuvant treatment with imatinib lasted for up to 3 years, in line with the maximum adjuvant treatment duration in the studies described in the summary of product characteristics.

The manufacturer did not submit any subgroups apart from patients classified at high risk of relapse according to the Miettinen criteria, noting that mutations and tumour biological factors are not considered established independent risk factors and are not included in the current risk-stratification schemes. The ERG stated that the manufacturer's approach to duration of treatment was consistent with the NICE

scope for this appraisal, which did not specify any duration of adjuvant imatinib treatment.

4 Clinical-effectiveness evidence

4.1 The manufacturer's systematic review identified 3 phase III randomised controlled trials that evaluated imatinib as adjuvant treatment for GIST: ACOSOC Z9001, the SSGXVIII/AIO study and EORTC 62024 (table 1). Twelve non-randomised trials were also identified, which are summarised in the manufacturer's submission and the manufacturer stated that the results generally supported those from the randomised controlled trials (see page 81 of the manufacturer's submission).

Table 1 Randomised controlled trials in the manufacturer's submission

Trial	Intervention	Comparator	Population	Risk of recurrence	Primary outcome	Key secondary outcomes
ACOSOG Z9001 (double-blind)	Imatinib 400 mg/day for 1 year (n=359)	Placebo for 1 year (n=354)	Adults with complete resection of c-KIT (CD117)-positive GIST	Any level	Recurrence -free survival (changed from overall survival)	Safety
SSGXVIII/AIO study (open-label, prospective)	Imatinib 400 mg/day for 1 year (n=199)	Imatinib 400 mg/day for 3 years (n=198)	Adults with c-KIT (CD117)-positive GIST removed at open surgery	High risk (based on modified US NIH Consensus Criteria)	Recurrence -free survival	Safety, overall survival
EORTC 62024 (open-label, observational)	Imatinib 400 mg/day for 2 years (n=454)	No other therapy after surgery (n=454)	Adults with resected localised, c-KIT (CD117)-positive GIST	Intermediate- or high-risk (defined by the NIH consensus criteria)	Imatinib-failure-free survival[a] (changed from overall survival)	Overall survival

[a] Imatinib failure-free survival: failure was defined as the time at which patients had to change to a different tyrosine kinase inhibitor because of disease relapse or recurrence

4.2 The manufacturer provided intention-to-treat analyses for recurrence-free survival and overall survival in ACOSOG Z9001, both for the full population and for a high risk population identified retrospectively using

the Miettinen 2006 criteria. At the time of the primary analysis, the study was unblinded and patients randomised to placebo who had not experienced disease recurrence (n=79) were allowed to cross over to treatment with imatinib for 1 year. Of these patients, 72 opted to cross over to receive 1 year of treatment with imatinib. The manufacturer also provided data from a 5-year follow-up analysis of ACOSOG Z9001 but noted that because these data were analysed according to intention-to-treat, they did not take into account the impact of treatment switching.

4.3 The manufacturer presented results from the SSGXVIII/AIO study based on an analysis of 397 of the 400 randomised. Patients in the study were considered to be at high risk of recurrence in line with the modified version of the NIH consensus criteria, but the manufacturer was also able to present post-hoc results for people at high-risk using the Miettinen 2006 criteria (n=281). The manufacturer considered the baseline patient and disease characteristics in ACOSOG Z9001 and the SSGXVIII/AIO study to be well balanced between treatment groups. Neither study recorded health-related quality of life.

4.4 Results for EORTC 62024 were presented from an interim analysis but the manufacturer stated that it was not possible to determine patients at high risk of recurrence in line with the Miettinen 2006 criteria. The manufacturer also stated that imatinib failure-free survival as a surrogate outcome for overall survival was different from other GIST trials. The manufacturer emphasised that robust conclusions on the effect of adjuvant therapy for 2 years on survival cannot be drawn from this interim analyses.

Results for the full trial populations

ACOSOG Z9001

4.5 At the primary outcome analysis of ACOSOG Z9001 (median follow-up 19.7 months), 1-year recurrence-free survival was estimated to be 98% (95% confidence interval [CI] 96 to 100) in the imatinib group and 83%

(95% CI 78 to 88) in the placebo group, which was a statistically significant difference (HR 0.35 [0.22 to 0.53], p<0.0001). Overall survival at 2 years was estimated to be 98.8% in the imatinib group and 97.6% in the placebo group, with a hazard ratio of 0.66 (95% CI 0.22 to 2.03), which was not statistically significant.

4.6 At the 5-year follow-up analysis of ACOSOG Z9001, approximately 75% of patients in both groups remained on study. The 5-year follow-up data showed estimated 5-year recurrence-free survival (median follow-up 46.3 months) was 72.8% (95% CI 67.1 to 78.4) in the imatinib group and 68.4% (95% CI 63.0 to 73.8) in the placebo group. Recurrence-free survival for imatinib was statistically significantly greater in the imatinib group compared with the placebo group during follow-up (hazard ratio 0.718 [95% CI 0.531 to 0.971], p=0.0305). The manufacturer advised that the follow-up analysis was confounded by patients who had been randomised to placebo and were recurrence-free at the time of study unblinding and had then opted to cross over to active treatment for 1 year. The manufacturer reported that a supporting analysis which removed these patients had a hazard ratio of 0.671 (95% CI 0.491 to 0.919, p=0.0123), but did not provide any further details about the methodology.

4.7 The 5-year follow-up analysis showed that 5-year overall survival (median follow-up of 60.2 months) in ACOSOG Z9001 was 91.3% for the imatinib group and 91.1% for the placebo group. There was no statistically significant difference in overall survival between treatment groups during follow-up (HR 0.816 [95% CI 0.488 to 1.365], p=0.4385). A sensitivity analysis that censored for patients eligible for crossover to 1 year of imatinib treatment gave a hazard ratio of 0.746 (95% CI 0.441 to 1.262, p=0.2725).

SSGXVIII/AIO study

4.8 Median duration of follow-up was 54 months for the full population. The median time to recurrence was 53.2 months for the 1-year imatinib group, but it was not reached for the 3-year imatinib group. Overall, recurrence-

free survival was statistically significantly longer in the 3-year group than the 1-year group (hazard ratio 0.46 [95% CI 0.32 to 0.65], p<0.0001; 5-year recurrence-free survival 65.6% and 47.9% respectively). There was no significant difference in the risk of recurrence or death between the 1-year and 3-year treatment groups during the first 1 year of treatment or after 3 years. However, a difference was evident from 1 to 2 years (hazard ratio 0.26 [95% CI 0.13 to 0.53]) and from 2 to 3 years (hazard ratio 0.17 [95% CI 0.07 to 0.39]) after randomisation.

4.9 Overall survival was statistically significantly greater in the in the 3-year imatinib group than in the 1-year imatinib group (hazard ratio 0.45 [95% CI 0.22 to 0.89], p=0.019; 5-year overall survival 92.0% and 81.7% respectively). However, there was no statistically significant difference in 5-year GIST-specific survival between the 2 groups (88.5% in the 3-year group compared with 95.1% in the 1-year group; hazard ratio 0.46 [95% CI 0.19 to 1.14], p=0.09).

EORTC 62024

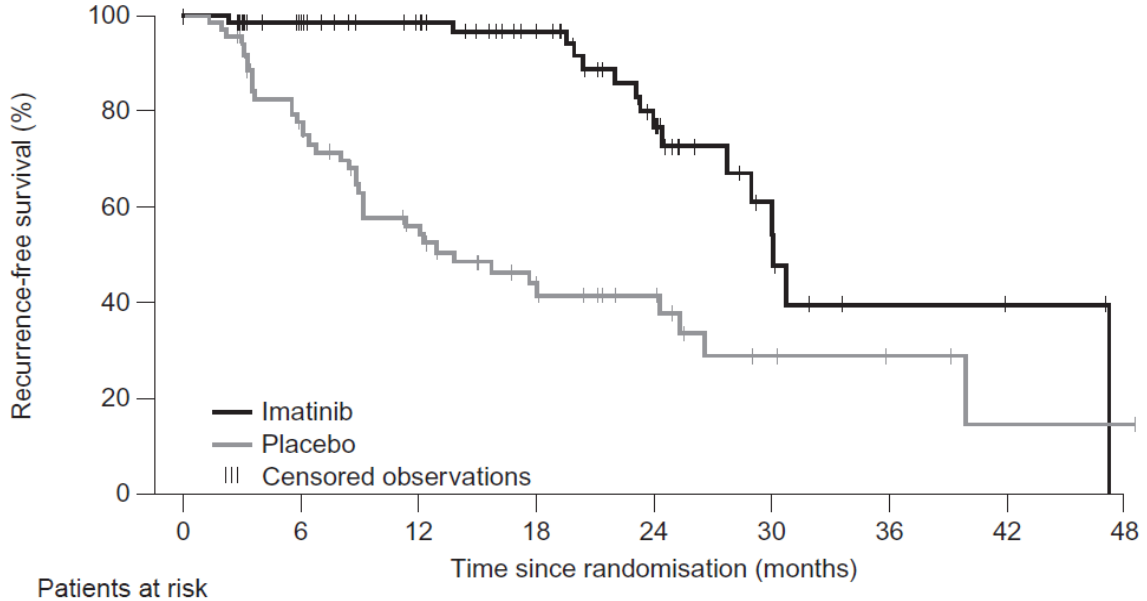
4.10 The EORTC 62024 interim analysis was for a median follow-up of 4.7 years. Of the 908 patients who had been randomised to treatment, 835 were eligible for assessment. Recurrence-free survival for the total study population was statistically significantly greater in the imatinib group compared with the observation group at 3 years (84% compared with 66%, p<0.001) and 5 years (69% compared with 63%, p<0.001). There were no statistically significant differences in 5-year imatinib-failure-free survival between the imatinib and observation groups (87% compared with 84%; hazard ratio 0.80 [98.5% CI 0.51 to 1.26], p=0.23). Overall survival at 5 years was similar in the imatinib and observation groups (100% and 99% respectively).

Results for high-risk subgroups (Miettinen 2006 criteria)

ACOSOG Z9001

4.11 Using the ACOSOG Z9001 primary analysis, the manufacturer identified 165 patients at high risk of disease recurrence according to Miettinen 2006 criteria. For these patients, 1-year recurrence-free survival was 98.7% in the imatinib group and 56.1% in the placebo group (figure 1). An analysis of overall survival revealed no statistically significant difference between treatment groups overall (p=0.0764). Overall survival at 2 years was 100% in the imatinib group and 94.7% in the placebo group; at 4 years it was 100% and 90.9%.

Figure 1 Recurrence-free survival in the Miettinen high-risk population in ACOSOG Z9001 (primary analysis)



Patients at risk

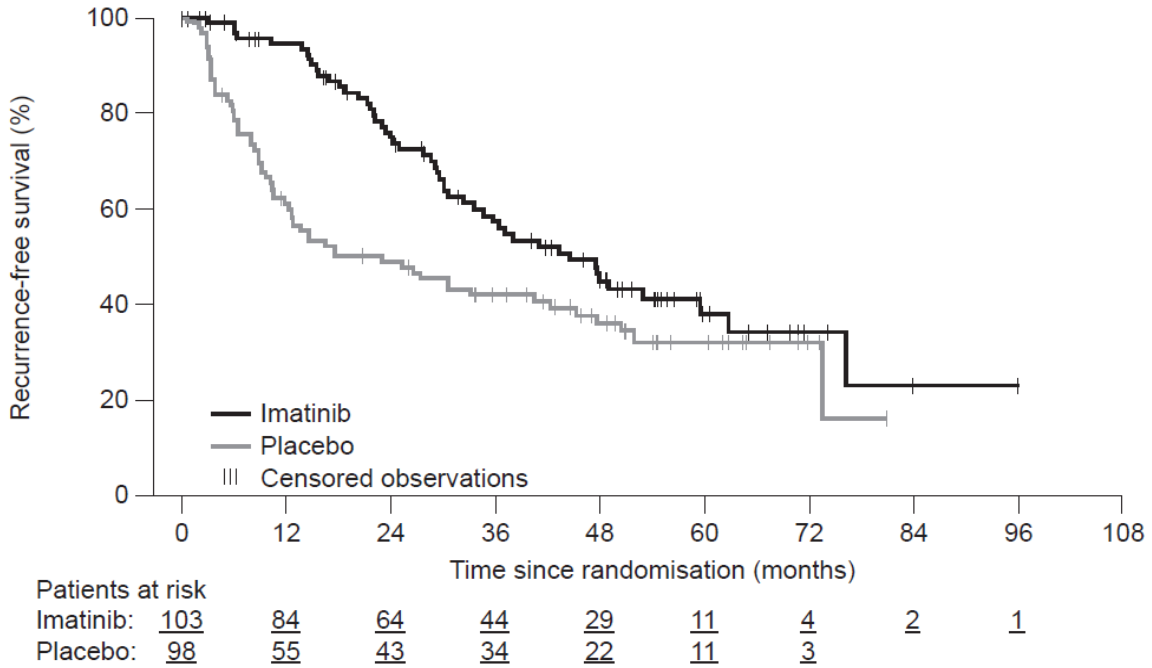
Imatinib:	84	62	53	42	25	9	3	2	
Placebo:	81	50	30	19	12	5	3	1	1

Source: page 68 of the manufacturer's submission

4.12 At the 5-year follow-up analysis, a total of 103 high-risk patients had been identified in the imatinib group and 98 patients in the placebo group. An improvement in recurrence-free survival was observed in the imatinib

group compared with placebo group (hazard ratio 0.608 [95% CI 0.417 to 0.886], p=0.009; figure 2). The difference between the imatinib and placebo groups was at its greatest 18 months after randomisation (86.7% [79.6 to 93.7] compared with 49.9% [39.7 to 60.2] respectively), and then decreased over time (reaching 37.9% [25.9 to 49.9] and 32.1% [21.6 to 42.6] respectively at 5 years). The manufacturer noted that, unlike the primary analysis, the 5-year follow-up analysis was confounded by placebo patients who were recurrence-free at the time of study unblinding opting to cross over to active treatment for 1 year.

Figure 2 Recurrence-free survival in the Miettinen high-risk population in ACOSOG Z9001 (5-year follow-up analysis)



Source: page 70 of the manufacturer's submission

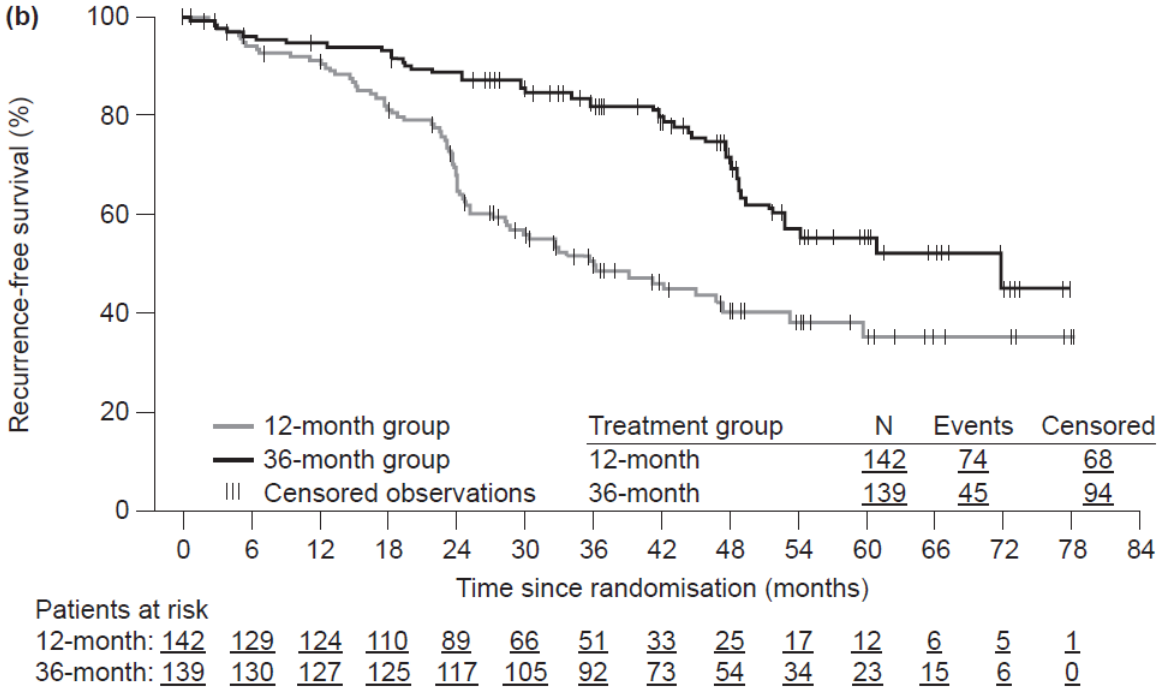
4.13 At the clarification stage, the manufacturer provided a report that used different methods of adjusting for treatment crossover in ACOSOG Z9001. The methods were a rank preserving structural failure time model, the iterative parameter estimation algorithm, inverse probability of censoring weights (IPCW), as well as per-protocol analyses that censored crossovers at the time of switching or excluded them altogether. The report concluded that the IPCW method was the most reliable for

recurrence-free survival and overall survival. In patients at high-risk of disease recurrence, the IPCW hazard ratio for recurrence-free survival was 0.50 (95% CI 0.3–0.78), which was similar to the simple, unweighted, per-protocol censoring approach (hazard ratio 0.52 [95% CI 0.35–0.77]). Both provide a numerically lower hazard ratio for recurrence-free survival than the intention-to-treat analysis (hazard ratio 0.61 [95% CI 0.42–0.89]). For overall survival, the IPCW hazard ratio in the high-risk group was 0.76 (95% CI 0.36–1.62), which was similar to the simple, unweighted per-protocol censoring approach (hazard ratio 0.79 [95% CI 0.40–1.55]). The report stated that these were numerically lower than the hazard ratio for the intention-to-treat analysis (0.93 [95% CI 0.47–1.83]).

SSGXVIII/AIO study

4.14 Overall, 70% of patients were at high risk of recurrence according to the Miettinen 2006 criteria (142 in the 1-year imatinib group and 139 in the 3-year imatinib group). At the 5-year follow-up, recurrence-free survival was longer in the 3-year group compared with the 1-year group (hazard ratio 0.43 [95% CI 0.30 to 0.62], $p<0.0001$; figure 3). Median time to recurrence was 35.9 months in the 1-year adjuvant imatinib group and 71.8 months in the 3-year adjuvant imatinib group.

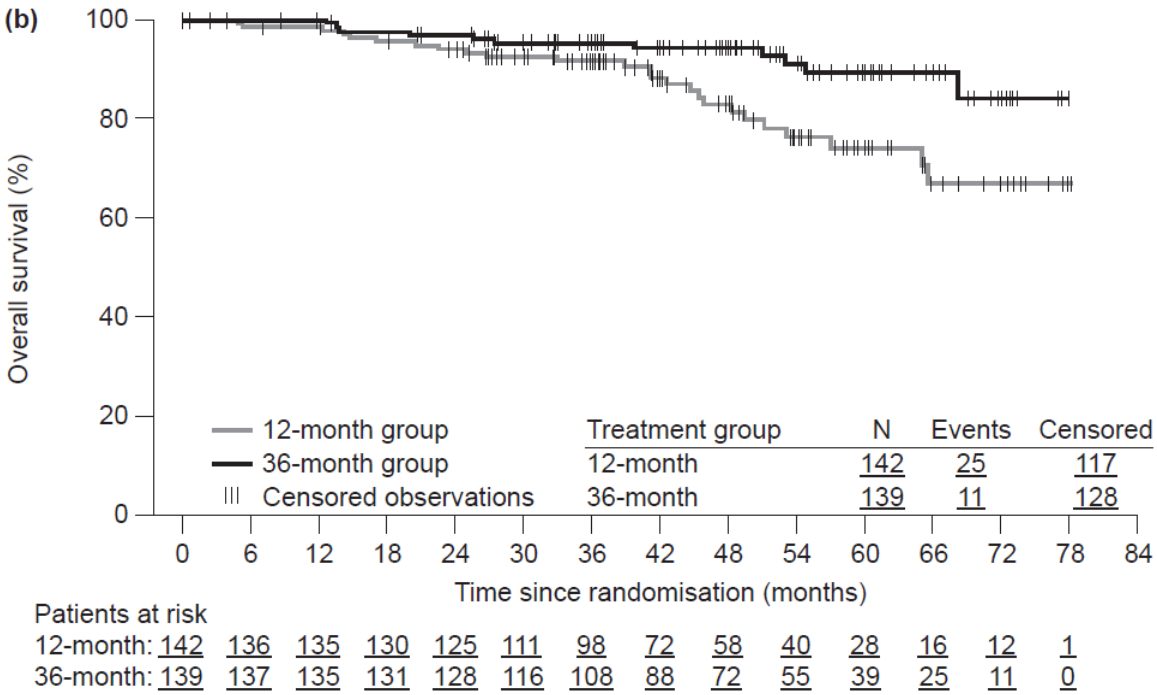
Figure 3 Recurrence-free survival in the Miettinen high-risk population in the SSGXVIII/AIO study



Source: page 74 of the manufacturer's submission

4.15 Overall survival was greater in the 3-year imatinib group compared with the 1-year imatinib group (hazard ratio 0.39 [95% CI 0.19 to 0.79], p=0.007; figure 4). Overall survival rates were higher with 3-year imatinib than 1-year imatinib at 4 years (94.5% [95% CI 88.6 to 97.3] compared with 83.0% [95% CI 73.8 to 89.1] respectively) and at 5 years (89.5% compared with 74.2%).

Figure 4 Overall survival in the Miettinen high-risk population in the SSGXVIII/AIO study



Source: page 76 of the manufacturer's submission

EORTC 62024

4.16 The EORTC 62024 interim analysis showed that for a subgroup of patients with high-risk disease according to the NIH consensus criteria, there was no statistically significant difference in 5-year imatinib failure-free survival between the imatinib and observation groups (77% and 73% respectively, p=0.44).

Indirect comparison

4.17 The manufacturer noted the absence of a head-to-head trial comparing no adjuvant treatment with 3 years of adjuvant imatinib, and considered the feasibility of an indirect comparison using a log hazard ratio with pairwise treatment comparisons, which assumes constant proportional hazards. However, after inspecting the Kaplan-Meier curves for recurrence-free survival in ACOSOG Z9001 and the SSGXVIII/AIO study, the manufacturer considered the shapes of the curves to be different for each treatment arm and that decided that the assumption of proportional

hazards did not hold. From this, it concluded that a simple parametric proportional hazards model fitted to these curves would not accurately estimate mean survival and did not conduct an indirect comparison using this method. For the purpose of the economic model, an indirect comparison using non-standard methodology was presented (see section 6.4).

Adverse events

4.18 In ASOCOG Z9001, grade 3 or 4 adverse events occurred in 104 patients (31%) in the imatinib group and 63 patients (18%) in the placebo group. The most common of these (imatinib versus placebo) were neutropenia (3% compared with 1%), abdominal pain (3.6% compared with 1.7%), dermatitis (3% compared with 0%), nausea (2.4% compared with 1.2%) and elevated alanine aminotransferase levels (2.7% compared with 0%). The manufacturer reported that the adverse event rate was consistent with imatinib use in chronic myelogenous leukaemia and metastatic GIST.

4.19 In the SSGVXIII/AIO study, the incidence of adverse events was similar in patients receiving imatinib for 3 years (198/198, 100%) and for 1 year (192/194, 99.0%). The incidence of grade 3 or 4 events was 20.1% in the 1-year group and 32.8% in the 3-year group, with leukopenia and diarrhoea being the most common. More patients in the 3-year group (51 patients, 25.8%) discontinued imatinib than in the 1-year group (25 patients, 12.9%).

4.20 No safety data from EORTC 62024 had been reported before the manufacturer provided its evidence submission.

ERG's comments

4.21 The ERG stated that the manufacturer's submission contained a generally unbiased estimate of imatinib's treatment effect, and noted that the randomised controlled trials had been well conducted (although 2 trials were open label and 2 had experienced a change in the primary outcome). It indicated that the main limitation of the clinical evidence was

that the treatment effect for high-risk patients was based on retrospective subgroup analyses, varying in the proportion of randomised patients (the lowest being 28%), meaning that these are most likely underpowered.

4.22 The ERG stated that differences in baseline patient characteristics between the treatment arms were more pronounced in the Miettinen high-risk subgroups in than the full trial populations, indicating selection bias. However, the ERG was unclear if the imbalances were statistically significant. Although results were similar for the full population and high-risk subgroups (in terms of significant recurrence-free and overall survival differences between trial arms), the ERG concluded that caution was necessary when interpreting the subgroup results.

4.23 The ERG highlighted that there were differences in the results for overall survival between ACOSOG Z9001 and the SSGXVIII/AIO study, and that neither of these trials was statistically powered to detect a difference in this outcome. In ACOSOG Z9001, there were few deaths overall and there was no statistically significant difference in overall survival for imatinib for 1 year compared with placebo at 2 years and 5 years. It further noted that even in the additional analyses that removed patients who had crossed over to active treatment, the difference between trial arms generally remained non-statistically significant. In the SSGXVIII/AIO study, there were comparatively more deaths and at 5 years there was statistically significantly longer overall survival associated with 3-year imatinib treatment compared with 1-year treatment. The ERG stated that although the differences in the overall death rates could potentially be explained by differences in patient characteristics (or other variables) between the 2 trials, the available evidence suggested that extending imatinib treatment to 3 years was associated with longer overall survival than 1-year treatment.

4.24 The ERG was concerned that the high degree of crossover at study unblinding in ACOSOG Z9001 may have led to confounding of the results and was aware that the manufacturer had presented analyses where

patients were censored at the time of crossover. The ERG also reviewed the supplemental report that used various statistical methods to adjust for patient crossover in ACOSOC Z9001, which was provided as part of the manufacturer's response to clarification. The ERG agreed that all the methods had advantages and limitations in the assumptions made and their applicability to ACOSOG Z9001, and that the IPCW method appeared to be appropriate. The ERG noted that all methods produced hazard ratios that were lower than the intention-to-treat analysis and therefore more favourable to imatinib. It also noted that the IPCW method produced hazard ratios that were similar to a per-protocol analysis that simply censors switchers at the time of crossover. The ERG considered this to be conservative because both of these approaches gave hazard ratios that were slightly lower (approximately 0.1 to 0.2) than the intention-to-treat analysis, compared with bigger differences for some of the other methods.

4.25 The ERG noted that though the manufacturer did not present subgroup analyses mentioned in the NICE scope, the SSGXVIII/AIO study reported recurrence-free survival for pre-defined exploratory subgroup analyses according to tumour site, tumour size and tumour mutation site for the full population discussed in the manufacturer's submission. The ERG noted, however, that no results for the high-risk group in the SSGXVIII/AIO study had been reported in the journal publication. The results of these subgroup analyses were similar to those of the full population. In the genetic mutational status subgroup, there was a statistically significant treatment effect favouring imatinib for 3 years for patients with the KIT exon 11 mutation, but not for other mutations or for patients with no mutation (but the numbers in these latter groups were smaller). The ERG advised that these analyses were exploratory and were likely to be underpowered.

5 Comments from other consultees

5.1 The patient organisations stated that a key benefit of imatinib treatment was increasing the time to disease recurrence. They noted that extending active life is extremely important to patients, and that being able to resume normal work and social interactions is highly valued. They stated that imatinib is generally well tolerated and the therapy required to control side-effects (such as oedema, rash and neutropenia) are well understood by doctors, nurses and patient support groups and considered to be manageable. They highlighted that because imatinib is an oral treatment, its ease of administration is patient friendly. A patient organisation observed that both imatinib groups (1 year and 3 years) in the SSGXVIII/AIO study tended to relapse after stopping adjuvant therapy, which raises questions about whether recurrence is being prevented or delayed.

5.2 A patient organisation explained that assessing who is at high risk of relapse is a crucial component of the use of adjuvant imatinib. The assessment tool that is most widely used at present was developed by Miettinen and Lasota (2006). This is based on tumour location, size, mitotic count and nature of surgery. However, it was emphasised that this is not the only tool that is used and that future developments are anticipated because of the growing importance of genetic profiling.

5.3 A clinical specialist and a patient organisation noted that certain GIST genotypes predict for sensitivity to imatinib (for example, KIT exon 11 mutant) whereas others are associated with resistance (for example, ‘wild type’ and PDGFRA D842V mutant). However, another patient organisation noted that there is no definitive indication that any of these groups will benefit more or less from adjuvant therapy. Currently, 4 NHS laboratories in England routinely perform GIST mutational analysis (which is not nationally funded) and it is not clear what proportion of patients have mutation analysis performed on their tumours to guide imatinib therapy. A potential consequence of adjuvant imatinib therapy becoming

standard practice would be increased demand for GIST mutational testing.

6 Cost-effectiveness evidence

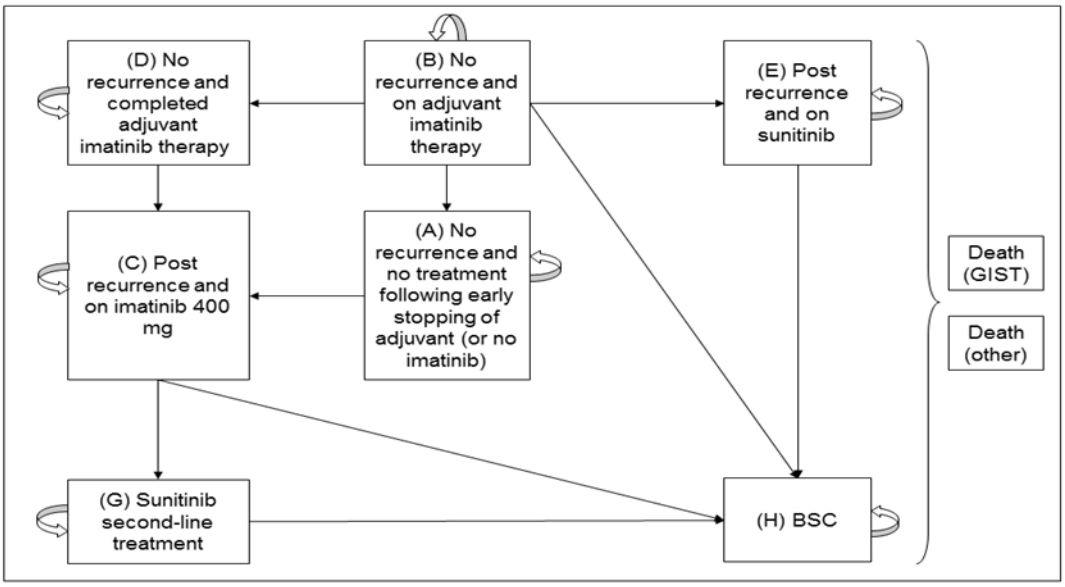
6.1 The manufacturer's cost-effectiveness analysis included patients at high risk of recurrence based on the Miettinen criteria (that is, a subset of the licensed indication described in section 2.1). The economic model compared adjuvant imatinib (1 or 3 years) after surgical resection with no adjuvant treatment. The manufacturer advised that this model was based on that submitted for NICE technology appraisal guidance 196 (that is, the guidance under review).

6.2 The manufacturer's model used a Markov state-transition approach (see figure 5). During each monthly cycle of the model, patients could:

- remain recurrence-free
- have a recurrent GIST (first or second recurrence)
- have progressive disease (and be treated with BSC) or
- die (from GIST or other causes).

Transition probabilities between the health states were based on the treatment-associated probabilities of recurrence or discontinuation. The model had a lifetime time horizon (50 years), a 1-month cycle length, and a discount rate of 3.5% was applied to costs and health effects. The analysis was conducted from an NHS and personal social services perspective.

Figure 5 Overview of manufacturer's model



6.3 All patients entering the model were recurrence-free after surgery. They received either observation or adjuvant imatinib (for 1 or 3 years), and progressed through the model as follows:

- Patients who experienced a first recurrence while taking adjuvant imatinib therapy were assumed to then receive sunitinib (90%) or best supportive care (10%).
- Patients who experienced a first recurrence after receiving surgical resection only, or after discontinuing or completing planned adjuvant imatinib treatment, received first-line imatinib (400 mg/day treatment). Patients who discontinued adjuvant imatinib because of adverse events were assumed to have the same rate of recurrence as patients remaining on adjuvant imatinib because these patients were not censored when calculating recurrence-free survival. The manufacturer assumed that 15% of patients had further surgery but this was not explicitly modelled (only costs were included, not effectiveness).
- After a second progression or recurrence, or discontinuation because of adverse events, most patients (90%) received sunitinib then best supportive care after further progression.
- Patients receiving best supportive care were assumed to have progressive disease and remained in this health state until death.

Moving between the different health states was dependent on the probabilities of events (recurrences, adverse events and death), which were taken from the SSGXVIII/AIO study, ACOSOG Z9001 and published sources.

6.4 Because there was no head-to-head trial directly comparing surgery alone with 3 years of adjuvant imatinib, the manufacturer conducted an indirect comparison using data from the SSGXVIII/AIO study and ACOSOG Z9001. It considered that the assumption of constant proportional hazards did not hold and so did not use the log hazard ratio with pairwise treatment comparisons (see section 4.17). Instead, the baseline risk of recurrence for patients treated with surgical resection only was taken from ACOSOG Z9001. A parametric survival model was fitted to patient-level data from the placebo arm of ACOSOG Z9001 using data from the primary analysis (that is, at study unblinding and before cross-over was allowed) and restricted to patients classified at high-risk of recurrence according to the Miettinen criteria. The Miettinen risk group for patients in this trial was derived from the 5-year follow-up analysis. The manufacturer examined goodness-of-fit visually and using AIC and BIC statistics, and assessed the extrapolation beyond the trial's duration for validity compared with the published results of other trials.

6.5 The manufacturer calculated a treatment effect for imatinib then applied it to the baseline risk of recurrence after surgical resection only to estimate the risk of recurrence for patients treated with adjuvant imatinib therapy after surgical resection. The treatment effect was estimated for 2 distinct periods: during treatment and immediately after stopping treatment, to capture the differences in events rates observed in each period:

- During treatment, the same effect for imatinib was assumed regardless of treatment duration (1 or 3 years), with an estimated hazard ratio of 0.111 (95% CI 0.043 to 0.281) for risk of recurrence compared with placebo. This was calculated from the hazard ratio for recurrence from

ACOSOG Z9001 using the Cox proportional hazards model with the data truncated at 12 months.

- After stopping treatment, when compared with placebo, the estimated hazard ratios were 0.519 (95% CI 0.297 to 0.906) for 1 year of adjuvant imatinib and 0.344 (95% CI 0.160 to 0.741) for 3 years of adjuvant imatinib. These were estimated using datasets of patients who had not experienced disease recurrence during adjuvant treatment. The modified dataset from ACOSOG Z9001 was used to calculate the hazard ratio for recurrence for 1-year adjuvant imatinib compared with surgery only and the modified dataset from SSGXVII/AIO was used to calculate the hazard ratio for recurrence for 3-year adjuvant imatinib compared with 1-year adjuvant imatinib. These estimates of treatment effect were then combined using a frequentist indirect comparison using a fixed effects model to estimate the hazard ratio for recurrence for 3 year adjuvant imatinib compared with surgery only.

To estimate the risk of recurrence for patients treated with surgical resection followed by 1 and 3 years of adjuvant imatinib, the manufacturer then applied the estimated treatment effect for imatinib (during and after stopping treatment) to the baseline risk of recurrence for patients treated with surgical resection only. In its clarification response, the manufacturer advised that resistance to imatinib was implicitly included in the economic model through the response rates obtained in the clinical trials (in the adjuvant and advanced settings).

6.6 Health-related quality of life was not recorded in ACOSOG Z9001 and the SSGXVIII/AIO study. The manufacturer did a systematic review, which identified 3 potentially relevant health-related quality of life publications, to derive the utility values for its economic model:

- The manufacturer assumed that GIST patients who had undergone successful surgical resection and were recurrence-free had the same utility as healthy individuals of the same age (0.822).

- Patients receiving adjuvant imatinib treatment had a utility value of 0.741 (a utility decrement of 0.081 was applied to all patients in the base case to reflect adverse effects).
- Patients receiving first-line treatment with imatinib or sunitinib (that is, after first recurrence) had a utility value of 0.739
- A utility value of 0.739 was also used for patients taking sunitinib after a second recurrence.
- The utility value for the best supportive care health state was 0.577.

For further details of the utility values used in the manufacturer's economic model, see pages 176–180 of the manufacturer's submission.

6.7 The manufacturer's literature review did not identify any primary studies estimating the resource use associated with treating GIST in the UK. Health state costs were derived from NHS reference costs, UK clinical guidelines and assumptions. The one-off onset cost of recurrence was £1430.69 and was assumed to include 1 GP visit, 1 specialist outpatient visit, 1 CT scan and, where appropriate, surgical resection (assumed to be 15% of patients). Annual costs of continuing phase of cancer (defined as the period between the first year after diagnosis and the last year of life) were estimated at £793.50 (an average of 2 GP visits, 5 outpatient visits and 0.5 CT scans). Costs for the last year of life were estimated to be £17,380. Drug costs for imatinib and sunitinib were taken from the British national formulary (October 2013), and the manufacturer incorporated the patient access scheme for the second-line use of sunitinib. Costs for treating adverse events with imatinib were based on the most frequent grade 3 and 4 adverse events in SSGXVIII/AIO (neutropenia, fatigue, nausea and vomiting, and diarrhoea). No costs were assumed for treating adverse effects in patients who received surgical resection only. For further details of the costs used in the manufacturer's economic model, see pages 187–196 of the manufacturer's submission.

6.8 The manufacturer's base-case results showed that adjuvant imatinib treatment (1 year and 3 years) was associated with greater QALY gains and higher costs than no adjuvant treatment (table 2). In the manufacturer's fully incremental analysis, the ICER for 1 year's treatment with imatinib compared with no adjuvant treatment was £3509 per QALY gained, while the ICER for 3 years' treatment with imatinib compared with 1 year was £16,006 per QALY gained (incremental costs £22,931; incremental QALYs 1.43).

Table 2 Manufacturer's base-case results

	Total costs	**Total QALYs**	**Total LYs**	**Incr. costs**	**Incr. QALYs**	**Incr. LYs**	**ICERs vs no treatment (£/QALY)**	**Fully incr. ICERs (£/QALY)**
No adjuvant treatment	£47,292	3.83	5.08					
Adjuvant imatinib for 1 year	£55,136	6.07	7.71	£7844	2.24	2.63	£3509	£3509
Adjuvant imatinib for 3 years	£78,068	7.50	9.46	£22,931	1.43	1.75	£8390	£16,006

Key: ICER, incremental cost-effectiveness ratio; incr., incremental; LY, life years; QALY, quality-adjusted life year
Source: page 220 of the manufacturer's submission

6.9 At the clarification stage, the manufacturer reproduced the base-case analysis using the 5-year follow-up data for recurrence-free survival for the placebo arm of ACOSOG Z9001, which did not adjust for the crossover of patients from placebo to imatinib. In the manufacturer's fully incremental analysis, the ICER for 1 year's treatment with imatinib compared with no adjuvant treatment was £8556 per QALY gained. The ICER for 3 years' treatment with imatinib compared with 1 year was £17,057 per QALY gained (incremental costs and QALYs not provided).

6.10 The manufacturer carried out a range of deterministic sensitivity analyses to test the model's structural assumptions and confirmed that the ICERs were insensitive to changes in costs, utility values and most transition probabilities. It reported that varying the 'on-treatment' and 'off-treatment'

hazard ratios according to their upper and lower confidence limits caused changes in the ICERs. It confirmed that when the upper limits for both were included the ICERs increased from £3509 per QALY gained to £30,058 per QALY gained for 1 year's treatment with imatinib compared with no adjuvant treatment, and from £16,006 per QALY gained to £29,162 per QALY gained for 3 years' treatment with imatinib compared with 1 year.

6.11 The manufacturer did probabilistic sensitivity analyses using 1000 iterations. Like the deterministic base-case analysis, these showed that adjuvant treatment with imatinib (1 year and 3 years) was associated with greater QALY gains and higher costs than no adjuvant treatment (table 3). For the pairwise comparisons with no adjuvant treatment, the ICER for 1 year's treatment with imatinib was £3635 per QALY gained (incremental costs £8375; incremental QALYs 4.62) and the ICER for 3 years' treatment with imatinib was £7950 per QALY gained (incremental costs £30,958; incremental QALYs 3.89). The manufacturer also provided a fully incremental analysis. The ICER for 1 year's treatment with imatinib compared with no adjuvant treatment remained at £3635 per QALY gained, while the ICER for 3 years' treatment with imatinib compared with 1 year was £14,205 per QALY gained (incremental costs £22,583; incremental QALYs 1.59). At a maximum acceptable ICER of £20,000 per QALY gained, the probability of imatinib being cost effective was 41.7% for 1 year's treatment and 58.3% for 3 years' treatment. When the maximum acceptable ICER was increased to £30,000 per QALY gained, the probability of 1 year's treatment with imatinib being cost effective decreased to 30.9%, whereas the probability of 3 years' imatinib treatment being cost effective rose to 69.1%.

Table 3 Manufacturer's probabilistic results

	Total costs	Total QALYs	Total LYs	Incr. costs	Incr. QALYs	Incr. LYs	ICERs vs no treatment (£/QALY)	Fully incr. ICERs (£/QALY)
No adjuvant treatment	£48,256	5.27	2.27					
Adjuvant imatinib for 1 year	£56,631	7.57	4.62	£8375	2.30	2.35	£3635	£3635
Adjuvant imatinib for 3 years	£79,214	9.16	6.21	£22,583	1.59	1.60	£7950	£14,205

Key: ICER, incremental cost-effectiveness ratio; incr., incremental; LY, life years; QALY, quality-adjusted life year
Source: page 227 of the manufacturer's submission

6.12 The manufacturer conducted scenario analyses to further explore uncertainty. It found that there was little impact on the ICERs for any of the following scenarios:

- Using different parametric distributions for the survival curves
- Allowing dose escalation of imatinib in the metastatic setting
- Varying the proportion of patients receiving best supportive care (instead of active treatment) after recurrence
- Extending survival in the post-recurrence health states.

The manufacturer stated that its sensitivity analyses showed the ICERs were fairly insensitive to changes in parameters and assumptions, with the ICERs generally remaining below £20,000 per QALY gained. It noted that key drivers of the model were treatment effect over time and the time horizon of the analysis, and that changes in these parameters cause some ICERs to exceed £20,000 per QALY gained.

6.13 In response to a request made at the clarification stage, the manufacturer provided scenario analyses that assumed imatinib's treatment effect declined over time during the off-treatment period. The manufacturer's ICERs for adjuvant imatinib (1 or 3 years) compared with no adjuvant treatment, and for adjuvant imatinib for 3 years compared with 1 year,

increased when the off-treatment hazard ratio was reduced to 75%, 50% or 25% after 5 years. The ICERs ranged from £4569 per QALY gained to £34,683 per QALY gained (table 4).

Table 4 Manufacturer's scenario analyses reducing the off-treatment hazard ratio after 5 years

	ICER after reducing HR to 75% (£/QALY gained)	ICER after reducing HR to 50% (£/QALY gained)	ICER after reducing HR to 25% (£/QALY gained)
Adjuvant imatinib for 1 year compared with no adjuvant treatment	£4569	£6831	£14,079
Adjuvant imatinib for 3 years compared with no adjuvant treatment	£9952	£13,210	£22,939
Adjuvant imatinib for 3 years compared with adjuvant imatinib for 1 year	£18,242	£22,735	£34,683

Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year
Source: page 14–16 of the manufacturer's clarification response

ERG's comments

6.14 The ERG stated that the model structure and methodology used by the manufacturer was a reasonable approach to modelling the cost effectiveness of imatinib as adjuvant treatment for GIST. It observed that the manufacturer had made some amendments to the model in response to comments during the original appraisal of imatinib as adjuvant treatment for GIST (NICE technology appraisal guidance 196). However, the ERG raised several concerns around the estimates and assumptions in the current model.

6.15 The ERG noted that the manufacturer's model did not explicitly model disease progression and instead defined the health states based on treatment. As a result, the ERG considered that some of the later progressions in the model did not seem appropriate (for example, patients discontinuing treatment because of adverse events may transition to best supportive care without experiencing disease recurrence).

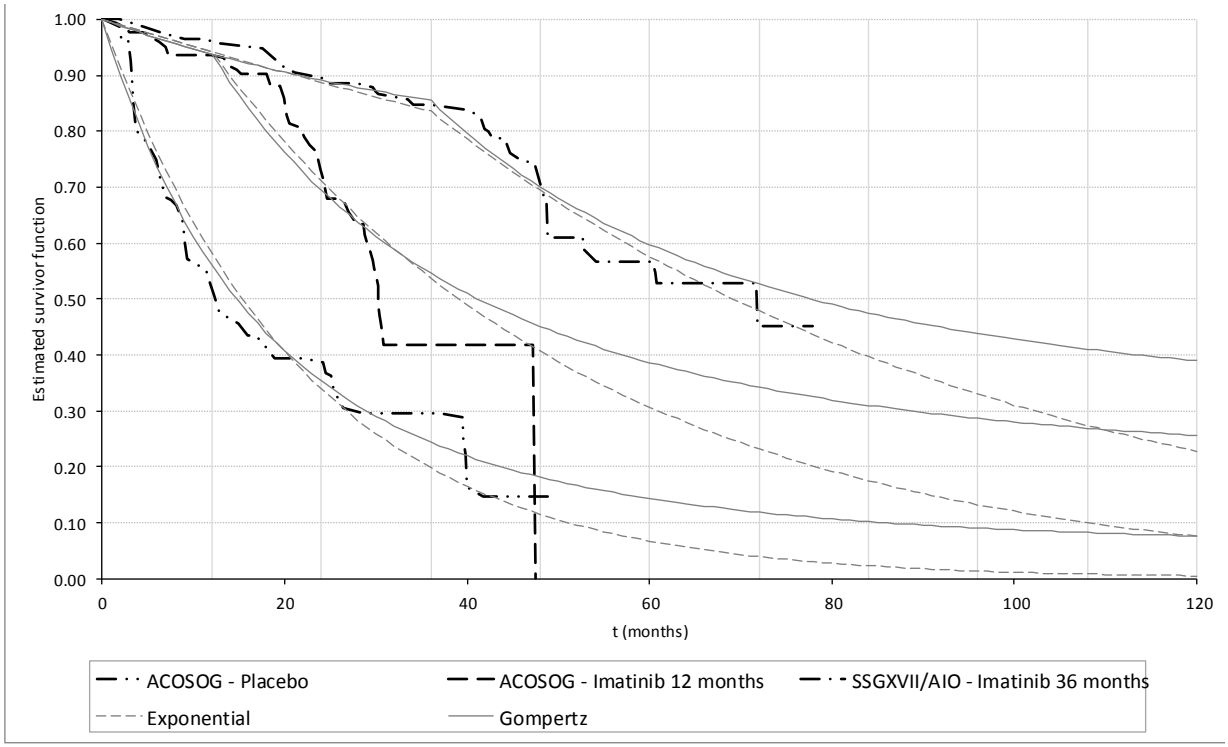
6.16 The ERG had reservations about the validity of some utility values. The ERG stated that although the majority of these were based on the only published set of values for patients with advanced GIST, insufficient methodological detail had been reported and there was a lack of information about respondents such as baseline characteristics of respondents, sample size, response rate or the valuation method adopted.

6.17 The ERG stated that there was substantial uncertainty over the manufacturer's methods used to derive the baseline risk of recurrence and relative treatment effects for adjuvant imatinib in its economic model. The ERG was aware that that the manufacturer had adopted these methods to avoid confounding by crossover in the placebo arm of ACOSOG Z9001. The ERG agreed that the Kaplan–Meier curves indicated changes in the shape of the survival curves after stopping adjuvant imatinib treatment, but stated that these trends might have been more apparent, and the cut–points more easily identified and justified, by plotting the hazard function rather than the Kaplan–Meier curves. Regarding the approach to estimating 'on-treatment' treatment effect, the ERG was concerned that the manufacturer had derived the treatment effects using a semi-parametric model (Cox proportional hazards) then applied these to fully parametric survival functions used to derive baseline risk of recurrence (that is, with surgery alone). The ERG noted that the on-treatment recurrence-free hazard ratio for the high-risk population, using the Cox proportional hazards model with the data truncated at 12 months, was 0.111 (95% CI, 0.043 to 0.281). The ERG noted that this was lower than the hazard ratio of 0.265 (95% CI 0.148 to 0.477) that was reported in the clinical-effectiveness section of the manufacturer's submission, and was unclear whether the difference was caused by truncating the data at 12 months or the retrospective re-classification of additional high risk patients. The ERG noted that the manufacturer's submission does not state clearly the maximum follow-up for placebo patients before cross-over (censoring) so it was unable to judge the duration over which the

baseline survival function was modelled. The ERG noted that the manufacturer's overall approach had required considerable post-hoc re-organisation of the trial data and was uncertain if this had introduced biases into the estimated effects. The ERG concluded that it may be more appropriate to use the crossover-adjusted recurrence-free survival estimates to derive clinical effectiveness parameters from ACOSOG Z9001.

6.18 The ERG also expressed substantial uncertainty about the most appropriate assumptions for extrapolating the effectiveness of adjuvant imatinib beyond the follow-up period of the randomised controlled trials providing baseline and relative treatment effects for adjuvant imatinib. The maximum follow-up in the randomised controlled clinical trials was around 9 years and these effects were extrapolated over a lifetime (40-year) time horizon in the model. In particular, the ERG was concerned about the face validity of these survival extrapolations based on the Gompertz function, which suggested a long-term maintenance of recurrence-free survival in around 30% of patients who received 3 years' adjuvant imatinib treatment. The ERG was concerned this may not be appropriate in a population initially identified as being at high risk of recurrence. This compares with approximately 20% recurrence-free survival at 20 years using the loglogistic model or approximately 5% using the other functions. The ERG provided a graph based on figures B-13 and B-20 in the manufacturer's submission, which showed how the projected survival rates differed for extrapolations based on the Gompertz function (used in the manufacturer's base case) compared with the exponential function (figure 6).

Figure 6 Alternative parametric explorations of the recurrence-free survival curves from ACOSOG Z9001 and SSGXVIII/AIO



6.19 The ERG assessed the validity of the results generated using the manufacturer's model compared with the clinical trials. The ERG considered that there was a reasonable fit for recurrence-free survival compared with the clinical trials at 5 years for patients who had received adjuvant imatinib (for 1 year or 3 years) and at 2 years for patients who had received no adjuvant treatment. However, the ERG considered the fit for overall survival to be poorer and noted that the manufacturer's model underestimated overall survival at 5 years for patients who had received 1- or 3-year adjuvant imatinib treatment, and at 2 years for patients who had received no adjuvant treatment. The ERG added that there was uncertainty around estimated long-term extrapolation of recurrence-free survival, and noted that long-term recurrence-free survival differed widely according to the parametric distribution chosen. The ERG noted that the parametric distribution chosen by the manufacturer produced the most favourable ICER for adjuvant imatinib treatment.

6.20 The ERG expressed uncertainty over the manufacturer's approach to incorporating costs for sunitinib on the model. It noted that the manufacturer estimated sunitinib use by allowing for a 21% probability of discontinuation per month, which resulted in an estimated mean duration

of treatment of 3.48 cycles. The ERG considered that the manufacturer had over-estimated sunitinib use because the 2 clinical trials for sunitinib reported a median of 2 cycles of treatment. Based on the clinical trial results, the ERG calculated that 2.89 cycles would be a more appropriate mean estimate for use in the model. Using the ERG's estimate instead of the manufacturer's reduced the monthly cost of sunitinib (with a patient access scheme) from £1615.34 to £1,231.17.

6.21 The ERG reviewed how the manufacturer had explored uncertainty in its economic model. It considered the parameters that were varied, and the ranges used, in the one-way sensitivity analyses to be appropriate and comprehensive. The ERG indicated that the manufacturer's probabilistic sensitivity analyses included most of the variables within the model, that the probability distributions had been correctly applied and that the methods used to assess parameter uncertainty were appropriate. Nevertheless, the ERG noted that the manufacturer's submission did not include variation around the cost of imatinib, or the proportion receiving sunitinib or best supportive care after recurrence.

ERG's exploratory analyses

6.22 The ERG identified some errors in the utility values and management costs used in the manufacturer's submission and provided corrected base-case results (table 5). In a fully incremental analysis, the ERG's ICER for 1-year imatinib treatment compared with no adjuvant treatment was £3612 per QALY gained (incremental costs £7819; incremental QALYs 2.16), while the ERG's ICER for 3 years' treatment with imatinib compared with 1 year was £16,663 per QALY gained (incremental costs £22,928; incremental QALYs 1.38). These corrected base-case ICERs were similar to the original base-case results provided by the manufacturer (see section 6.8).

Table 5 ERG's correction of the manufacturer's base case

	Total costs	Total QALYs	Incr. costs	Incr. QALYs	Fully incr. ICERs (£/QALY)
No treatment	£46,962	3.83			
Adjuvant imatinib 1-year treatment	£54,780	6.00	£7819	2.16	£3612
Adjuvant imatinib 3-year treatment	£77,708	7.37	£22,928	1.38	£16,663

Key: ICER, incremental cost-effectiveness ratio; incr., incremental; QALY, quality-adjusted life year
Source: page 95 of the ERG report

6.23 The ERG explored issues and uncertainties that it had identified in the manufacturer's submission, including the assumption of a continuing off-treatment effect of adjuvant imatinib, the parametric distribution used for modelling recurrence-free survival, resistance to imatinib and the mortality estimates used for the recurrence health states (table 6). The ERG did the following analyses:

- Assumed no long-term off-treatment benefit after the reported follow-up, and reported that changing this assumption did not markedly alter the cost-effectiveness results.
- Used the exponential distribution to model recurrence-free survival and found that the ICERs increased to £9386 per QALY gained for 1-year adjuvant imatinib treatment compared with no treatment and to £18,741 per QALY gained for 3-year compared with 1-year imatinib treatment.
- Investigated the effect of varying the off-treatment hazard ratio for 1-year imatinib treatment compared with no adjuvant treatment, but maintaining the hazard ratio for 3-year compared 1-year imatinib treatment. The ERG reported that the ICERs were very sensitive to changes in the off-treatment hazard ratio for the 1-year adjuvant imatinib treatment compared no adjuvant treatment:
  - The ERG ran the analysis using the 95% upper confidence interval of the 5-year update unadjusted hazard ratio estimate of 0.727 (provided by the manufacturer at the clarification stage)

  - It found that the ICER for 1-year adjuvant imatinib treatment compared with no adjuvant treatment increased to £10,489 per QALY gained.
- Investigated the effect of assuming resistance to imatinib developing at recurrence in 15% of patients who were initially treated with adjuvant imatinib. Patients who were assumed not to respond to re-treatment progressed to sunitinib. This assumption produced marginal changes to the ICERs.
- Varied the mortality rate by using the lower confidence interval estimates for GIST mortality in the post-recurrence health states, which slightly reduced the ICER for the 1-year adjuvant imatinib compared with no treatment.
- Assumed that 15% of patients initially treated with adjuvant imatinib and re-challenged upon recurrence would not respond (based upon SSGXVIII/AIO data), and would then receive sunitinib. This produced marginal changes in the ICERs.

The ERG then ran an analysis that combined several of these factors (no treatment benefit after the end of trial, exponential distribution for recurrence-free survival and lower mortality rates). This increased the ICERs to £12,122 per QALY gained for 1-year adjuvant treatment compared with no treatment and £29,966 per QALY gained for 3-year treatment compared with 1-year treatment.

Table 6 ERG's exploratory analyses

	No treatment		1-year adjuvant imatinib		3-year adjuvant imatinib		ICER (cost per QALY)		
	Total costs	Total QALYs	Total costs	Total QALYs	Total costs	Total QALYs	1 year vs no treatment	3 years vs 1 year	3 years vs no treatment
Corrected base case	£46,962	3.83	£54,780	6.00	£77,708	7.37	£3612	£16,663	£8684
No extended benefit	£44,823	4.30	£54,780	6.00	£77,466	7.41	£5854	£15,995	£10,465
Exponential dist. used for RFS	£49,546	3.26	£62,464	4.63	£86,211	5.90	£9386	£18,741	£13,871
HR off treatment 0.906[a]	£46,962	3.83	£61,675	4.44	£84,484	6.02	£24,252	£14,393	£17,123
HR off treatment 0.727[a]	£46,962	3.83	£59,255	5.00	£81,865	6.55	£10,489	£14,582	£12,820
Imatinib resistance[b]	£46,962	3.83	£52,394	5.93	£76,279	7.33	£2591	£17,018	£8377
Lower mortality rates[c]	£65,251	4.76	£68,328	6.69	£87,715	7.90	£1595	£16,112	£7171
Combined analysis[d]	£67,603	4.53	£79,205	5.49	£102,087	6.25	£12,122	£29,966	£20,041

[a] HR shown for the off treatment period for 1-year adjuvant imatinib versus no treatment. [b] 15% of patients, initially treated with adjuvant imatinib, develop resistance [c] Using lower confidence interval estimates for post recurrence health states. [d] Analysis has no off treatment benefit after the end of trial, exponential distribution for the RFS, and lower mortality rates.

7 Equality issues

7.1 No potential equality issues were identified during the scoping process or in any of the submissions, and none had been previously identified in NICE technology appraisal guidance 196.

8 Innovation

8.1 The manufacturer stated that imatinib is an innovative therapy that targets a key pathological driver in GIST. After complete resection, most recurrences occur within 5 years. Using adjuvant imatinib in patients at high risk of relapse offers increased recurrence-free survival and overall

survival to patients who would not otherwise be offered post-surgical therapy. It further noted that the availability of longer-term follow-up data for adjuvant imatinib treatment given up to 3 years, now support the benefits of continued treatment, and should allow imatinib to be recognised as offering a step change in the management of patients known to be at high risk of disease recurrence after surgery.

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Imatinib for the adjuvant treatment of gastrointestinal stromal tumours. NICE technology appraisal guidance 196 (2010).
- Sunitinib for the treatment of gastrointestinal stromal tumours. NICE technology appraisal guidance 179 (2009).
- Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours. NICE technology appraisal guidance 86 (2004).

NICE pathways

- There is a NICE pathway on gastrointestinal cancers.

Appendix B: Clinical efficacy section of the draft European public assessment report

9.1 The variation assessment report for the extension of the imatinib marketing authorisation to include the adjuvant treatment of adult patients following resection of Kit (CD117)-positive GIST can be found here.