



CED-CCO Special Advice Report #17

Imatinib mesylate in the adjuvant treatment of gastrointestinal stromal tumours (GIST)

T. Asmis, A.E. Haynes, C. Swallow, and S. Verma

Report Date: May 31, 2010

SUMMARY

The full CED-CCO Special Advice Report #17 consists of a Summary and a Full Report and is available on the CCO website (<http://www.cancercare.on.ca>) PEBC CED-CCO page at: <http://www.cancercare.on.ca/toolbox/qualityguidelines/other-reports/evaldrug-rep/>

QUESTIONS

1. Does the use of imatinib mesylate (imatinib; Gleevec®) as adjuvant treatment in adult patients with primary, non-metastatic, resected gastrointestinal stromal tumour (GIST) expressing the c-Kit tyrosine kinase receptor result in improved outcomes?
2. Which subgroups of patients benefit from the use of adjuvant imatinib following resection of primary, non-metastatic GIST?

Outcomes of interest include overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS), response, quality of life, and adverse effects.

TARGET POPULATION

Adult patients with primary, non-metastatic resected GIST expressing c-Kit (identified by CD117 immunohistochemical staining).

RECOMMENDATIONS

The following recommendations reflect the opinions of the authors of this special advice report.

- For patients with completely resected, primary, non-metastatic GIST expressing c-Kit, the use of adjuvant imatinib following surgery is recommended to improve RFS.

QUALIFYING STATEMENTS

- It is important to note that in the identified randomized controlled trial (RCT), patients were stratified according to tumour size, and in a post-hoc analysis, the predominant benefit of RFS was observed in patients with ≥ 6 cm GIST.
- Until further evidence is available, the recommended dose of imatinib mesylate is 400 mg daily for one year.

KEY EVIDENCE

One double-blind RCT of adjuvant imatinib compared to placebo in patients with resected, primary, non-metastatic GIST was identified (1). The authors reported a significant difference in RFS in favour of adjuvant imatinib: estimated one-year RFS for adjuvant imatinib versus [vs.] placebo, 98% vs. 83%; hazard ratio (HR), 0.35; 95% confidence interval (CI), 0.22-0.53; $p < 0.0001$. In a post hoc analysis, the predominant benefit of RFS was observed in patients with ≥ 6 cm GIST. Although the authors did not report whether differences in adverse events were statistically significant or not, it is important to note that higher rates of both any grade and grade 3/4 neutropenia, fatigue, dermatitis, nausea, vomiting, diarrhea, alanine aminotransferase, aspartate aminotransferase, and edema were observed for patients who received adjuvant imatinib compared to patients who received placebo.

FUTURE RESEARCH

There are two ongoing RCTs that have completed enrolment. The Scandinavian study (SSGXVIII) is a randomized trial of adjuvant imatinib in resected high-risk GIST. The patients were randomized between 12 or 36 months of therapy, and the outcome was RFS. The European Organization for Research and Treatment of Cancer (EORTC) 62024 study is a randomized trial of adjuvant imatinib in resected GIST in which the patients were randomized between control and 24 months of imatinib. Both these studies will address whether more than one year of adjuvant therapy is optimal.

IMPLICATIONS FOR POLICY

The data has shown that patients who have primary, non-metastatic, resected GIST now have an effective adjuvant therapy that will improve RFS. An estimated 50% of recurrences are unresectable and incurable, and a widely held belief is that efforts to reduce the chance of recurrence is clinically significant and will likely lead to an improvement in OS. Until future studies addressing the impact of adjuvant therapy on OS are completed, RFS is an appropriate and clinically relevant outcome. Imatinib has not demonstrated significant benefit in patients at low risk of relapse, and until further data is available, there is consensus that adjuvant therapy should be considered in patients at high risk of relapse.

RELATED PROGRAM IN EVIDENCE-BASED CARE GUIDELINES

Evidence-based Series

- #11-7: *Imatinib Mesylate (Gleevec™) for the Treatment of Adult Patients with Unresectable or Metastatic Gastrointestinal Stromal Tumours.*
Available at:
<http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/sarcoma-eb/>.

CED-CCO SPECIAL ADVICE REPORT #17

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Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775

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FULL REPORT

QUESTIONS

1. Does the use of imatinib mesylate (imatinib; Gleevec®) as adjuvant treatment in adult patients with primary, non-metastatic, resected gastrointestinal stromal tumour (GIST) expressing the c-Kit tyrosine kinase receptor result in improved outcomes?
2. Which subgroups of patients benefit from the use of adjuvant imatinib following resection of primary, non-metastatic, resected GIST?

Outcomes of interest include overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS), response, quality of life, and adverse effects.

INTRODUCTION

GIST is the most common sarcoma of the gastrointestinal tract. Complete surgical resection is the only curative treatment for GIST. However, despite optimal surgery, there remains a high risk of recurrence, and without adjuvant therapy, Dematteo et al found a five-year survival of 54% (1). Risk factors for recurrence include tumour size, mitotic count, and location of the tumour (2). These observations led the American College of Surgeons Oncology Group (ACOSOG) to perform the phase III study of adjuvant therapy in resected GIST.

METHODS

This advice report, produced by the CCO Program in Evidence-based Care (PEBC), is a convenient and up-to-date source of the best available evidence on the adjuvant use of imatinib in patients with primary, non-metastatic, resected GIST, developed through a systematic review of the available evidence. Contributing authors disclosed any potential conflicts of interest. The PEBC is editorially independent of the Ontario Ministry of Health and Long-Term Care.

The PEBC has a formal standardized process to ensure the currency of each clinical guidance report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original clinical guidance report information.

Literature Search Strategy

MEDLINE (Ovid) (1996 to January Week 4 [February 8], 2010), EMBASE (Ovid) (1996 to Week 5 [February 8], 2010), and the Cochrane Library (February 2010) databases were searched. The search strategies for MEDLINE and EMBASE are shown in Appendix 1. Search strategies in other databases were similar.

In addition, conference proceedings of the Annual Meetings of the American Society of Clinical Oncology (ASCO) (2004-2009) and the ASCO Gastrointestinal Cancers Symposium (ASCO GI) (2007-2009) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>), the National Guidelines Clearinghouse (<http://www.guideline.gov/index.asp>), and the National Institute for Clinical Excellence (<http://www.nice.org.uk/>) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials. Personal files were also searched.

Study Selection Criteria

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were published full report articles or published meeting abstracts involving:

1. Randomized trials that compared the adjuvant use of imatinib following surgical resection to either surgical resection alone or surgery and placebo.
2. Patients with primary, non-metastatic, resected GIST expressing the c-KIT tyrosine kinase receptor.
3. Systematic reviews, meta-analyses, or clinical practice guidelines on the use of adjuvant imatinib following surgical resection in patients with primary, non-metastatic, resected GIST.
4. Publications of randomized trials, systematic reviews, or meta-analyses reporting data on one or more of the following outcomes: OS, DFS, RFS, response rate, quality of life, or adverse events.

Exclusion Criteria

Studies were excluded if they were:

1. Letters, comments, books, notes, or editorial publication types.
2. Articles published in a language other than English, because of financial considerations for translation.

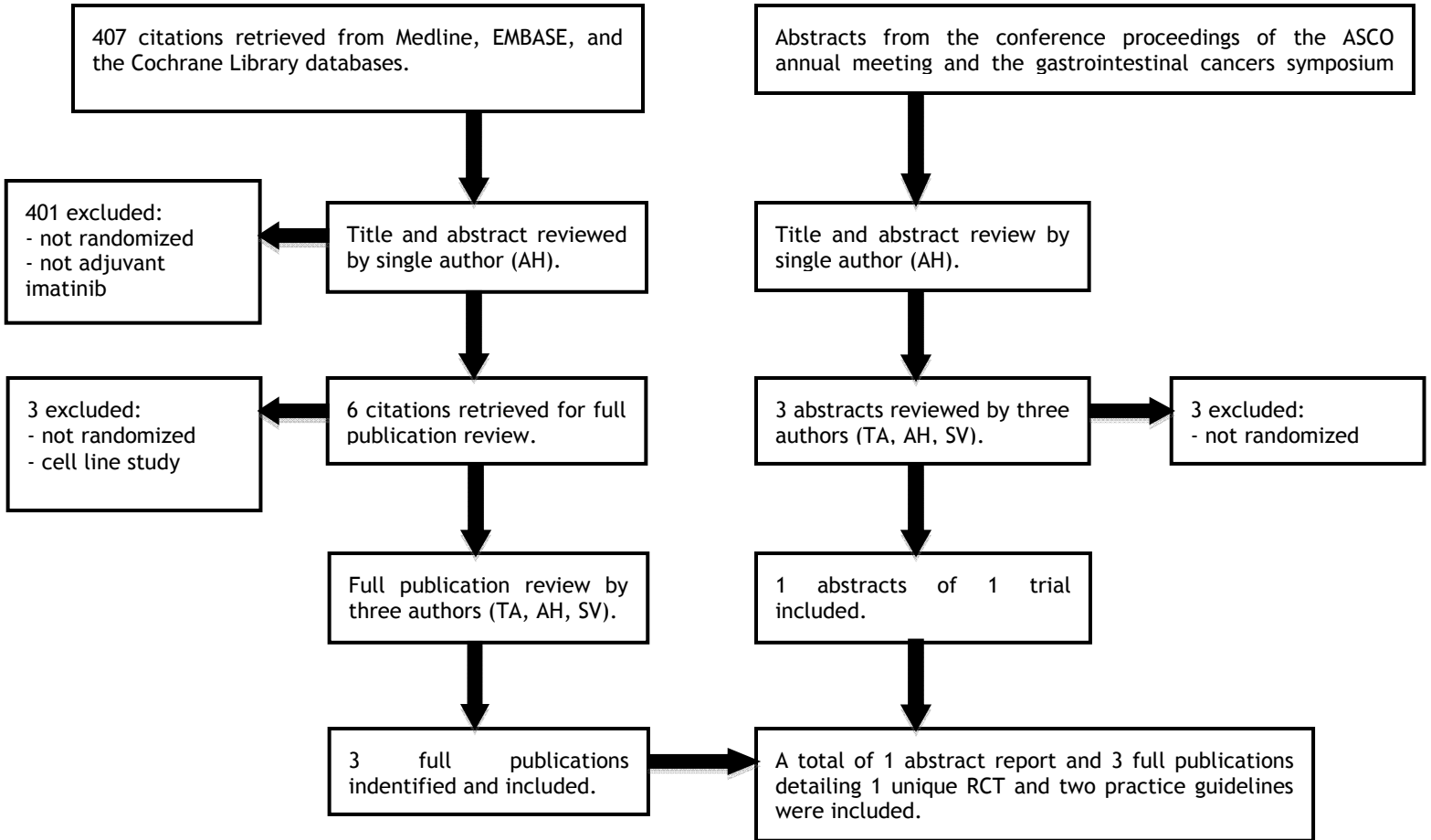
Synthesizing the Evidence

A meta-analysis was not done as only one trial was identified that met the eligibility criteria.

RESULTS

A total of 407 citations were identified from the MEDLINE, EMBASE, and the Cochrane Library databases. From those citations, a total of six full publications were retrieved for full review. Three publications met our eligibility criteria (Figure 1); two were clinical practice guidelines (3,4), and one was an RCT (5). In addition, only one abstract (6) was identified that met our eligibility criteria (Figure 1); that abstract was an early publication of the fully published RCT (5).

Figure 1. Selection of studies investigating the use of adjuvant imatinib in GIST from the search results of the MEDLINE, EMBASE, and Cochrane Library databases and the conference proceedings of ASCO.



Practice Guidelines

Two clinical practice guidelines were identified that investigated the use of adjuvant imatinib following resection of primary, non-metastatic disease (3,4). Although Nishida et al (3) identified a report detailing the early results of a double-blind, placebo-controlled RCT of adjuvant imatinib that indicated prolonged RFS in favour of adjuvant imatinib, the authors did not make a recommendation for or against the use of adjuvant imatinib in primary, non-metastatic, resected GIST, because the trial was still ongoing. The guideline was not included in further deliberations relating to this CED report.

The National Comprehensive Cancer Network (NCCN) published an updated guideline on soft tissue sarcoma in 2009 (4). The authors did not provide the methods used to develop the guideline, nor did they indicate whether a systematic search of the literature was undertaken. The NCCN guideline was not considered further, given the lack of reporting of methods.

Randomized Controlled Trials

One RCT of adjuvant imatinib in patients with primary, non-metastatic, resected GIST was identified (5).

Trial and Patient Characteristics

DeMatteo et al (5) reported the results of a phase III double-blind RCT comparing one year of adjuvant imatinib to one year of placebo (Table 1). The two arms were similar for a number of demographic and baseline disease characteristics (5).

Table 1. Patient and intervention details for RCTs of adjuvant imatinib in GIST.

Author, year (ref)	Patient characteristics	Treatment	Differences between treatment groups at baseline
DeMatteo, 2009 (5)	Histologically diagnosed, CD117+, localized, primary GIST measuring ≥ 3 cm, completely resected within 70 days of registration. Patient age ≥ 18 years, ECOG PS ≤ 2	Imatinib 400 mg/day for 1 year Placebo once daily for 1 year	Arms balanced

Notes: ECOG=Eastern Cooperative Oncology Group; GIST=gastrointestinal stromal tumour; PS=performance status; ref=reference.

Trial Quality

The quality characteristics of the randomized trial can be found in Table 2. The primary outcome was RFS, which was defined as the time from patient registration to the development of tumour recurrence or death from any cause (5). OS was a secondary outcome. The authors used an appropriate randomized method and concealed treatment allocation, and both investigators and patients were blinded to the arm that the patient was assigned. During randomization, patients were stratified by tumour size to one of three groups: ≥ 3 cm but < 6 cm, ≥ 6 cm but < 10 cm, or ≥ 10 cm. The original endpoint for the study was OS; however, the original design overestimated the event rate (death) because imatinib had just begun clinical trials in the metastatic setting when the trial was designed. As the trial progressed, it became clear to the authors that the actual event rate would be substantially lower than originally estimated due to the efficacy of imatinib in recurrent GIST and the crossover design of the study that allowed patients who progressed while on placebo

to receive imatinib. After discussions between the trial authors and the United States (US) Food and Drug Administration (FDA) the primary endpoint was changed to RFS. The authors estimated that the median RFS for patients receiving placebo would be 3.5 years, based on historical data. The trial would be required to accrue 600 additional patients over 2.5 years for a total of 803 patients, with a minimum follow-up of three years to provide 90% power at a one-sided alpha of 0.025 to detect an improvement in RFS of 40% in the imatinib group (median, 4.9 years; hazard ratio [HR], 0.71). Interim analyses were to be conducted every six months. A truncated O'Brien-Fleming boundary was used to monitor treatment efficacy with an alpha of 0.0025 at every interim analysis. Accrual to the trial was stopped early based on a recommendation from the data and safety monitoring committee, because the trial results crossed the interim analysis efficacy boundary for the primary outcome. The final analysis was based on the intent-to-treat principle and includes data collected until the last day of accrual. The authors did not report the number of patients lost to follow-up.

Table 2. Quality characteristics of identified RCT.

Author, year (ref)	Primary outcome	Required sample size	Secondary outcomes	Randomization method	Allocation concealment	Blinding	ITT analysis	Final analysis	Early termination	Losses to follow-up	Ethical Approval
DeMatteo, 2009 (5)	RFS	803 pts req'd to detect a 40% improvement in RFS (placebo mdn 3.5y vs. imatinib mdn 4.9y) with a one-sided alpha of 0.025 and power of 90%.	OS	Centralized stratified biased coin design	Yes	Yes ¹	Yes	Yes	Yes ²	NR	Yes

Notes: HR=hazard ratio; ITT=intent-to-treat; mdn=median; NR=not reported; OS=overall survival; pts=patients; ref=reference; RFS=recurrence-free survival; req'd=required; trtmt=treatment; y=years.

¹Patients and investigators.

²Trial accrual was stopped early based on a recommendation from the data and safety monitoring committee because the trial results crossed the interim analysis efficacy boundary for RFS.

Outcomes

Survival Outcomes

Data for survival-based outcomes can be found in Table 3a.

Table 3a. Efficacy outcomes for RCT of adjuvant imatinib in GIST.

Author, year (ref)	Treatment	N	RFS	OS	Follow-up (months)
DeMatteo, 2009 (5)	Imatinib	359	<u>1 year</u> 98%	NR	19.7
	Placebo	354	83% HR=0.35; p<0.0001 95% CI 0.22-0.53	NR HR=0.66; p=0.47 95% CI 0.22-2.03	

Notes: CI=confidence interval; HR=hazard ratio; N=number randomized; NR=not reported; OS=overall survival; ref=reference; RFS=recurrence-free survival.

The authors reported a significant difference in the altered primary outcome, RFS in favour of adjuvant imatinib compared to placebo (estimated one-year RFS 98% versus [vs.] 83%; HR, 0.35; p<0.0001) (5). No significant difference in OS was detected (HR, 0.66; p=0.47); however, the trial was underpowered to detect a difference in that outcome.

Of note, the authors reported subgroup analyses of RFS, analysed by tumour size (3 cm to <6 cm; 6 cm to <10 cm; ≥10 cm); the results can be found in Table 3b.

Table 3b. One-year recurrence-free survival by tumour size.

Author, year (ref)	Treatment	N	3 cm to <6 cm	6 cm to <10 cm	≥10 cm	Follow-up (months)
DeMatteo, 2009 (5)	Imatinib	359	100%	99%	91%	19.7
	Placebo	354	92% HR=0.23; p=0.011 95% CI 0.07-0.79	84% HR=0.50; p=0.041 95% CI 0.25-0.98	65% HR=0.29; p<0.0001 95% CI 0.16-0.55	

Notes: CI=confidence interval; HR=hazard ratio; N=number randomized; NR=not reported; ref=reference; RFS=recurrence-free survival.

Toxicity

Data on any grade adverse events can be found in Table 4. Additional data on grade 3/4 adverse events can be found in Table 5. The data appear to show a trend toward an increase in any grade of neutropenia, fatigue, dermatitis, nausea, vomiting, alanine aminotransferase (ALT), aspartate aminotransferase (AST), edema, and hypokalemia for patients receiving imatinib. The data also appear to show a trend toward an increase in grade 3/4 neutropenia, fatigue, dermatitis, abdominal pain, nausea, vomiting, diarrhea, ALT, AST, edema, and syncope. It is important to note that the authors did not report if any of the differences in adverse event rates were statistically significant (5).

Table 4. Any adverse events in RCT of adjuvant imatinib in GIST.

Author, year (ref)	Treatment	N	Neutropenia (%)	Fatigue (%)	Dermatitis (%)	Abdominal pain (%)	Nausea (%)	Vomiting (%)	Diarrhea (%)	ALT (%)	AST (%)	Edema (%)	Hyper-glycemia (%)	Hypokalemia (%)	Syncope (%)	Dyspnea (%)
DeMatteo, 2009 (5)	Imatinib	337	18	57	35	26	53	26	59	17	12	77	11	9	1	5
	Placebo	345	7	41	20	27	28	14	29	14	9	30	14	4	>1	7

Notes: ALT=alanine aminotransferase; AST=aspartate aminotransferase; N=number evaluable; ref=reference.

Table 5. Grade 3 or 4 adverse events in RCT of adjuvant imatinib in GIST.

Author, year (ref)	Treatment	N	Neutropenia (%)	Fatigue (%)	Dermatitis (%)	Abdominal pain (%)	Nausea (%)	Vomiting (%)	Diarrhea (%)	ALT (%)	AST (%)	Edema (%)	Hyper-glycemia (%)	Hypokalemia (%)	Syncope (%)	Dyspnea (%)
DeMatteo, 2009 (5)	Imatinib	337	4	2	3	4	2	2	3	3	2	2	1	1	1	1
	Placebo	345	1	1	0	2	1	1	1	0	0	<1	2	1	0	1

Notes: ALT=alanine aminotransferase; AST=aspartate aminotransferase; N=number evaluable; ref=reference.

DISCUSSION

Only one RCT of adjuvant imatinib in patients with primary, non-metastatic, resected GIST was identified. The trial was high quality and demonstrated improved RFS in favour of adjuvant imatinib following surgery compared to placebo (HR, 0.35; 95% confidence interval, 0.22-0.53). Many of the side effects observed in the imatinib group were as expected and are not considered alarming. It is important to note that, in this trial, patients were stratified according to the size of tumour, and in a post hoc analysis, the predominant benefit of RFS was observed in patients with ≥ 6 cm GIST. It is increasingly recognized that the risk of relapse is dependent on a number of other factors, including the location of the primary, mitotic index, and mutation status; however, the impact of these factors on adjuvant treatment remain to be validated in future or ongoing trials. From a practical perspective, the authors believe that patients at a substantial risk of relapse ($\geq 20\%$), as per Miettinen criteria (7), should be considered for adjuvant treatment with imatinib.

The primary outcome was changed to RFS in the identified RCT. There is no evidence to date that RFS is directly associated with OS in GIST. However given the possibility that in high-risk GIST patients up to 50% of relapses may be unresectable or associated with major GI morbidities, there is increasing consensus that RFS is an important clinical outcome.

CONCLUSIONS

This randomized trial has shown that adjuvant therapy in patients who have had a completely resected, primary, non-metastatic GIST results in improved RFS.

ONGOING TRIALS

On the Internet, the National Cancer Institute Clinical Trials database (http://www.cancer.gov/search/clinical_trials/) and the National Institutes of Health Clinical Trials database (<http://clinicaltrials.gov/>) were searched for reports of new or ongoing randomized trials investigating the adjuvant use of imatinib in patients with primary, non-metastatic GIST. Appendix 2 provides details of the identified ongoing trials.

CONFLICT OF INTEREST

The authors of this special advice report disclosed potential conflicts of interest relating to the topic of this special advice report. Three authors declared grant and/or research support from Novartis (TA, CS, and SV). The remaining author (AH) reported no conflicts of interest.

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7. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol.* 2006;23(2):70-83.

Appendix 1. Literature search strategies.

Ovid MEDLINE

1. imatinib:.mp.
2. gleevec:.mp.
3. glivec:.mp.
4. or/1-3
5. gastrointestinal stromal tumo?r\$.mp.
6. gist:.mp.
7. gastrointestinal stromal tumor/
8. or/5-7
9. 4 and 8
10. meta-analysis as topic/
11. meta analysis.pt.
12. meta analy\$.tw.
13. metaanaly\$.tw.
14. (systematic adj (review\$1 or overview\$1)).tw.
15. or/10-14
16. Cochrane.ab.
17. embase.ab.
18. (cinahl or cinhal).ab.
19. science citation index.ab.
20. bids.ab.
21. cancerlit.ab.
22. or/16-21
23. reference list\$.ab.
24. bibliography\$.ab.
25. hand-search\$.ab.
26. relevant journals.ab.
27. manual search\$.ab.
28. or/23-27
29. selection criteria.ab.
30. data extraction.ab.
31. 29 or 30
32. review.pt.
33. review literature as topic/
34. 32 or 33
35. 31 and 34
36. comment.pt.
37. letter.pt.
38. editorial.pt.
39. or/36-38
40. 15 or 22 or 28 or 35
41. 40 not 39
42. randomized controlled trials as topic/
43. randomized controlled trial.pt.
44. random allocation/
45. double blind method/
46. single blind method/
47. clinical trials, phase III as topic/

48. clinical trial, phase III.pt.
49. clinical trials, phase II as topic/
50. clinical trial, phase II.pt.
51. (clinic\$ adj trial\$1).tw.
52. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw.
53. placebos/
54. placebo\$.tw.
55. (allocated adj2 random\$).tw.
56. random allocation.tw.
57. randomly allocated.tw.
58. or/42-57
59. case report.tw.
60. letter.pt.
61. historical article.pt.
62. or/59-61
63. 58 not 62
64. 41 or 63
65. practice guideline/
66. practice guideline\$.mp.
67. 65 or 66
68. 64 or 67
69. 9 and 68
70. limit 69 to (English language and humans)

Ovid EMBASE

1. exp imatinib/
2. imatinib:.mp.
3. gleevec:.mp.
4. glivec:.mp.
5. or/1-4
6. exp gastrointestinal stromal tumor/
7. gastrointestinal stromal tumo?r\$.mp.
8. gist:.mp.
9. or/6-8
10. 5 and 9
11. exp meta-analysis/
12. ((meta adj analy\$) or metaanaly\$).tw.
13. (systematic adj (review\$1 or overview\$1)).tw.
14. or/11-13
15. cancerlit.ab.
16. Cochrane.ab.
17. embase.ab.
18. (cinahl or cinhal).ab.
19. science citation index.ab.
20. bids.ab.
21. or/15-20
22. reference list\$.ab.
23. bibliography\$.ab.
24. hand-search\$.ab.
25. manual search\$.ab.

26. relevant journals.ab.
27. or/22-26
28. data extraction.ab.
29. selection criteria.ab.
30. 28 or 29
31. review.pt.
32. 30 and 31
33. letter.pt.
34. editorial.pt.
35. 33 or 34
36. 14 or 21 or 27 or 32
37. 36 not 35
38. randomized controlled trial/
39. randomization/
40. single blind procedure/
41. double blind procedure/
42. placebo/
43. randomi?ed control\$ trial\$.tw.
44. rct.tw.
45. random allocation.tw.
46. randomly allocated.tw.
47. allocated randomly.tw.
48. (allocated adj2 random\$).tw.
49. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw.
50. placebo\$.tw.
51. or/38-50
52. case study/
53. case report.tw.
54. abstract report/
55. letter/
56. or/52-55
57. 51 not 56
58. exp practice guideline/
59. practice guideline\$.tw.
60. 58 or 59
61. 37 or 57 or 60
62. 10 and 61
63. limit 62 to (human and English language)

Appendix 2. Ongoing trials.

A prospective, randomized, phase III study of preoperative plus postoperative imatinib mesylate (Gleevec, formerly STI-571) in patients with primary, recurrent, or metastatic resectable, c-Kit-expressing, gastrointestinal stromal tumour (GIST).

Patients: histologically confirmed, locally advanced and/or metastatic GIST with complete or partial resection planned.

Protocol ID:	NCT00500188
Last date modified:	February 24, 2010
Trial type:	Open-label uncontrolled randomized trial
Accrual:	48 patients
Primary outcome:	Response
Sponsorship:	M.D. Anderson Cancer Centre
Status:	Ongoing, not recruiting patients

Short (12 months) versus long (36 months) duration of adjuvant treatment with the tyrosine kinase inhibitor imatinib mesylate of operable GIST with a high risk of recurrence.

Patients: histologically confirmed, resectable GIST.

Protocol ID:	NCT00116935
Last date modified:	February 3, 2009
Accrual:	400 patients
Trial type:	Open-label randomized trial with active control
Primary outcome:	Recurrence-free survival
Sponsorship:	Scandinavian Sarcoma Group
Status:	Ongoing, not recruiting patients

Intermediate and high risk localized, completely resected, gastrointestinal stromal tumours (GIST) expressing KIT receptor: a controlled randomized trial on adjuvant imatinib mesylate (Glivec) versus no further therapy after complete surgery.

Patients: histologically confirmed, localized GIST that was completely resected two weeks to three months before study entry.

Protocol ID:	NCT00103168
Last date modified:	December 13, 2009
Trial type:	Open-label randomized trial with active control
Accrual:	750 patients
Primary outcome:	Overall survival
Sponsorship:	European Organization for the Research and Treatment of Cancer
Status:	Recruiting