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Evidence-based Series 11-8 Version 2 EDUCATION AND INFORMATION 2015

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Sunitinib Malate for Gastrointestinal Stromal Tumour (GIST) in Imatinib Mesylate Resistant Patients

Members of the Sarcoma Disease Site Group

An assessment conducted in October 2015 put Evidence-based Series (EBS) 11-8 Version 2 in the Education and Information Section. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardize process to ensure the currency of each document (PEBC Assessment & Review Protocol)

The reviewed EBS report, which is available on the CCO Web site, consists of the following three sections:

Section 1: Recommendations and Evidence (ENDORSED)
Section 2: EBS Development Methods and External Review Process
Section 3: Document Review Summary and Review Tool

Release Date: January 15, 2014

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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version June 2009	1996-2008	Full Report	Web publication	NA
Current Version 2 Jan 2014	2008- 2013	New data found in Section 3: Document Summary and Review Tool	Updated Web publication	2009 recommendations is **ENDORSED**

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Evidence-Based Series 11-8 Version 2: Section 1

Sunitinib Malate for Gastrointestinal Stromal Tumour (GIST) in Imatinib Mesylate Resistant Patients: Recommendations and Evidence

J. Younus, S. Verma, J. Franek, N Coakley, and the Sarcoma Disease Site Group

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: January 15, 2014

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 3: Document Review Summary and Tool for a summary of updated evidence published between 2008 and 2013, and for details on how this Clinical Practice Guideline was ENDORSED.

INTRODUCTION

Gastrointestinal stromal tumours (GISTs) are rare mesenchymal tumours of the gastrointestinal tract characterized by unique histological and immuno-histochemical features, including over-expression of the c-kit receptor. In patients with resectable disease, surgery is the mainstay of treatment. However, in patients with unresectable or metastatic disease, therapy with the tyrosine kinase inhibitor (TKI) imatinib mesylate (IM), marketed as Gleevec™, is the therapy of choice. The efficacy and toxicity of IM in this setting has been previously reviewed by the Sarcoma Disease Site Group (DSG) (1). While IM has irrevocably altered the course of GIST with a significant improvement in time to progression (TTP) and median overall survival (OS), when compared to historical data) it is by no means curative therapy, and most patients eventually progress. In such circumstances, patients who have demonstrated a prior response to IM at the usual starting dose of 400 mg/day are escalated to 800 mg/day as up to one third may exhibit stable disease through such as strategy. However, in those patients who progress on initial therapy with IM (approximately 15%) or in those who progress following dose escalation, therapeutic options are extremely limited.

The success of IM has provoked the development of an array of TKIs, of which sunitinib malate (SM), marketed as Sutent, is the most advanced in clinical trials. SM is an oral agent which inhibits phosphorylation of multiple tyrosine kinases, including c-kit, platelet derived growth factor receptor (PDGFR), and vascular endothelial growth factor receptor (VEGFR),

and as such, was a logical agent to study in GIST. Due to the high efficacy of IM in this disease, it was thought to be medically and ethically appropriate to study SM in patients who had primary resistance or intolerance to IM or in those who had progressed after an optimal exposure to IM (including an escalated dose). The Sarcoma DSG has therefore undertaken a review of the evidence to address the following question.

QUESTION

Is sunitinib malate (marketed as Sutent) superior to placebo or other intervention for primary outcomes of interest in adult patients with gastrointestinal stromal tumour(s) who have developed resistance or exhibit intolerance to imatinib mesylate?

INTENDED AUDIENCE

This guideline is meant for use by clinicians directly involved in the treatment of the target population.

TARGET POPULATION

Adult patients with unresectable or metastatic/recurrent GIST who have been previously treated with, and subsequently developed resistance or intolerance to IM.

OUTCOMES OF INTEREST

Outcomes of interest include TTP, OS and toxicity. While the impact on OS is the most influential outcome in terms of driving policy, outcomes such as TTP or progression-free survival (PFS) are increasingly valued in oncology trials dealing with metastatic disease. Such outcomes may in fact be the only signals of benefit in randomized trials where event-driven interim analyses lead to the unblinding of treatment arms or the crossover of patients between arms, or where other interventions that might affect post-trial survival are employed. In previous trials examining patients with unresectable/metastatic GIST, TTP has been suggested as an appropriate endpoint. The Sarcoma DSG acknowledges that clinicians, patients, and regulators must increasingly consider surrogates such as TTP to guide practice and inform policy where appropriate.

RECOMMENDATIONS AND KEY EVIDENCE

Recommendations

Sunitinib malate, administered at a dose of 50 mg/day in six-week cycles (four weeks on, two weeks off), is a recommended treatment option in patients with unresectable or metastatic/recurrent GIST who demonstrate:

- **Early progression at any time during the first 6 months while on optimum doses of imatinib mesylate (as measured by RECIST criteria)**
- **Progression following treatment with imatinib mesylate in doses of 400 - 1600 mg/day for an appropriate duration (as measured by RECIST criteria)***
- **Intolerance to imatinib**

Treatment should continue in six-week cycles until progression or intolerance. Patients should be encouraged to participate in appropriate clinical trials.

*** The Sarcoma DSG does not advise escalating doses of imatinib mesylate beyond 800 mg/day due to toxicity concerns.**

Key Evidence

- One double-blind, multicentre, randomized controlled trial (RCT) by Demetri et al. (2) examined the use of sunitinib malate in the target population. Results reported here were derived at the time of a first, planned interim analysis:

- In 312 patients randomized 2:1 (207 SM to 105 placebo), median TTP (primary endpoint) was significantly longer in patients treated with SM than in those treated with placebo at the time of a planned, first interim analysis (27.3 versus [vs.] 6.4 weeks, hazard ratio [HR] 0.33, 95% confidence interval [CI] 0.23-0.47, p<0.0001). Similar HRs in favour of sunitinib malate were reported in stratified analyses and in Cox proportional hazard models when controlling for baseline factors.
- Patients treated with SM had longer PFS (24.1 vs. 6.0 weeks, HR 0.33, 95% CI 0.24-0.47, p<0.001) and improved OS (HR 0.49, 95% CI 0.29-0.83, p=0.007, absolute difference in weeks not reported) (2).

Additional Evidence

The analysis reported by Demetri et al. (2) above under Key Evidence also included the following results:

- SM therapy induced partial response (PR) in 6.8% of patients and durable stable disease (SD≥22 weeks; deemed clinically significant) in 17.4% vs. 0% PR and 1.9% SD in placebo patients (3). The objective response rate (ORR) was significantly higher in patients treated with SM (7.0% vs. 0%, 95% CI 3.7-11.1%, p=0.006) (2). Four of nine IM-resistant patients achieved PR with sunitinib malate therapy, whereas none of four IM-resistant patients achieved PR with placebo (3).
- There was no difference in quality of life (QOL) as measured by EuroQol Visual Analog Scale (EQ-VAS) scores between the SM therapy arm and placebo over time. A non-significant trend towards higher pain relief response rate was observed for the SM group over placebo in the intention-to-treat (ITT) population (17.4% vs. 9.5%, p=0.064) and in patients who reported pain or analgesic use at baseline (31.0% vs. 17.2%, p=0.052) (3).
- SM therapy was generally well tolerated. The most frequent of all adverse effects (AEs) experienced in greater proportion by patients on SM over placebo were Grade 1/2 leucopenia (52% vs. 5%), neutropenia (43% vs. 4%), and thrombocytopenia (36% vs. 4%). Grade 3 hematological AEs were also reported more frequently in the SM group, including leucopenia (4% vs. 0%), neutropenia (8% vs. 4%), lymphopenia (9% vs. 2%), and thrombocytopenia (4% vs. 0%). P-values were not reported for toxicity comparisons.
- Regarding non-hematological AEs, the incidence of Grade 1-3 fatigue was greater for the SM group in comparison to placebo (34% vs. 22%). Other Grade 3 treatment-related non-hematological AEs that occurred more frequently on sunitinib malate included hand-foot syndrome (4% vs. 0%), diarrhea (3% vs. 0%), and hypertension (3% vs. 0%). No grade 4 AEs were observed.
- Patients who were intolerant to IM on study entry did not experience recurrence of previous toxic effects when on SM.
- No patients had clinical evidence of congestive heart failure, pancreatitis, or a mean decrease in left ventricular ejection (2).

A presentation from the 2006 American Society of Clinical Oncology (ASCO) annual meetings (3) provides updated data on immediate vs. delayed SM treatment following placebo patient crossover in the trial by Demetri et al. (see Qualifying Statements). The presentation reported that non-significant increases in median TTP (28.9 vs. 24.3 weeks, HR 0.90, 95% CI 0.52-1.54, p=0.691) and in OS (HR 0.76, 95%CI 0.54-1.06, p=0.107) were observed in patients who received immediate SM treatment versus delayed treatment. By the time of TTP and survival analysis, 70% (83/118) of placebo patients had crossed over to SM treatment. Placebo patient crossover did not alter the toxicity profile.

Qualifying Statements

- This review addresses the results of a single trial presented across several publications. The trial was stopped early following a planned interim analysis. Subjects were unblinded and allowed to cross over from placebo to SM. Notwithstanding the ethical considerations that should be taken into account in such settings, there is growing concern in the literature over trials that are stopped prematurely, and clinicians should interpret results of this trial only after understanding the methodological concerns (see Discussion).
- Resistance to IM was defined by progression as denoted by RECIST criteria. Thresholds for progression as bulleted in the above recommendations, for example, early progression (within six months) while on IM, and progression following treatment with escalated doses of IM (up to 1600 mg), were established both according to the entry criteria of the trial under review and based on prior knowledge and standard practice with IM for recurrent/metastatic GIST (see Discussion).
- While the Sarcoma DSG recommends SM for patients with resistance to IM on escalated doses of 1600 mg (as per trial entry criteria), the DSG does not actually recommend escalating IM doses beyond 800 mg because of concerns with toxicity (1).
- In the original trial report by Demetri et al. (2):
    - At the time of documented disease progression, treatment assignments were unblinded. Placebo patients were given the option of switching to SM, while those patients who were already receiving SM were given the opportunity to continue treatment at the investigator's discretion. As a result, and when considering the short follow-up time, the difference in OS between treatment group may have been reduced at the time of the first, planned interim analysis.
    - Study populations were analyzed according to ITT principles (all patients as randomized according to original randomization scheme), modified ITT (all ITT patients with disease progression on IM, and per protocol (all patients who received at least one dose of assigned study treatment). ITT data were reported for all efficacy measures and per protocol for safety.
- In the updated presentation from the 2006 ASCO annual meeting (3):
    - Updated analyses included placebo patients who had crossed over to sunitinib malate treatment following the favourable results observed for median TTP at the time of the first, planned interim analysis (as noted above). Thus, any updated analyses reflect immediate versus delayed sunitinib malate treatment and not SM versus placebo as the original trial data reported.
    - The delayed treatment arm for updated TTP analyses included only those patients originally randomized to placebo who crossed over to receive SM treatment prior to any disease progression, hence the low sample size (n=24).
    - Because the placebo patient crossover altered planned trial methodology, no statistical adjustments for prior interim analyses were necessary for the updated data.

SYSTEMATIC REVIEW METHODS AND RESULTS

This evidence-based series, produced by the Program in Evidence-Based Care (PEBC), is a convenient and up-to-date source of the best available evidence on the role of SM for GIST. For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by two members (JY & SV) of the PEBC Sarcoma Disease Site Group (DSG) and one methodologist (JF).

The body of evidence in this review is comprised entirely of one published phase III randomized controlled trial and related abstracts presented at the 2003-2006 ASCO annual meetings. That evidence forms the basis of a clinical practice guideline developed by the Sarcoma DSG and published at http://www.cancercare.on.ca. The practice guideline is

intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

MEDLINE (1996 through April 14, 2008), EMBASE (1996 through April 14, 2008), and the Cochrane Central Register of Controlled Trials (CENTRAL, 1996 through April 14, 2008) were searched for relevant articles. Search terms included treatment-specific search terms such as "sunitinib malate", or Sutent", or "SU11248", combined with disease-specific terms such as "GIST" or "gastrointestinal stromal tumour". The MEDLINE and EMBASE search strategies are available in Appendix A.

In addition, the 2003-2007 conference proceedings of the American Clinical Society of Oncology (ASCO) annual meetings (http://www.asco.org/) were searched for abstracts of relevant trials. The National Medical Association InfoBase (http://mdm.ca/cpgsnew/cpgs/index.asp), National Guideline Clearinghouse (http://www.guideline.gov/), and the National Institute for Health and Clinical Excellence (http://www.nice.org.uk/page.aspx?o=home) were also searched for existing evidenced-based guidelines, but no existing guidelines were found.

Study Selection Criteria

Inclusion Criteria

Articles were eligible for inclusion if they met the following criteria:

- SM as treatment for adult patients (≥15 years of age) with GIST was evaluated in a randomized phase III controlled clinical trial.
- Clinical trial reports were published as full peer-reviewed articles or publicly-available abstracts or presentations.
- Data reported on one or more of the following outcomes: ORR, TTP, SD rate, PFS, OS, toxicity, or QOL.

Exclusion Criteria

Articles were excluded if they were non-randomized phase I or II clinical trials, retrospective studies, editorials, letters, or articles. Any articles published in languages other than English were also excluded as translation capabilities were not available.

Synthesizing the Evidence

Data were not pooled as only one trial was available.

Literature Search Results

The literature search results identified one phase III randomized controlled trial (RCT) by Demetri et al. in full publication (2). No existing practice guidelines or systematic reviews were found. Four abstracts were identified which described the phase III randomized trial by Demetri et al (3-6). These abstracts were presented at the ASCO 2005 (5) and 2006 (4,6-7) annual meetings. Three accompanying presentations were also identified (3,8-9). Only one of the abstracts (4), and its accompanying presentation (3), updated trial results beyond the original full publication trial reports of the study by Demetri et al (2). The other abstracts (5-7), presented inutile or redundant data and thus are not further reported or discussed here. All important details and data from the identified reports are presented under Key Evidence and Additional Evidence, above.

DISCUSSION

In patients with unresectable or metastatic GISTs, therapy with IM at an initial dose of 400 mg/day is the recommended standard of care (1). Complete responses with IM are rare; the majority of patients exhibit partial responses, with progression observed after a median of two years. In such patients, the recommendation is that IM be escalated to 800 mg/day. Furthermore, patients who progress early (≤6 months) on conventional-dose IM (400 mg/day) do not derive any benefit from dose escalation and are thus presented with limited therapeutic options (1). For these patients, or others progressing at any point along the treatment continuum, there are salvage therapies available, including surgery or radioablation for areas of localized progression. As such therapies have not been consistently or prospectively evaluated, it is difficult to comment with confidence on their benefit. As a consequence, there have been no widely accepted or standard second-line (post-IM) therapeutic options available until now.

The study of SM versus placebo by Demitri et al. (2) is the only RCT of a TKI in the second-line setting for patients with advanced GISTs. Trial data confidently show that both TTP and PFS are highly statistically significant ($p<0.0001$) in favour of SM when compared to placebo. SM is therefore a recommended option for the second-line therapy of metastatic GIST for the target population. Despite the promising results, there are, however, some important methodological concerns that must be addressed when interpreting the results of this study.

The choice of a placebo as the comparator might be considered inappropriate, possibly biasing results in favour of SM. However, in the absence of any other widely applied second-line approach, including best supportive care, and in light of concerns over the potential side effects (harms) of escalated IM doses for all patients (>800 mg/day) or of cascading multiple-TKIs, a placebo-controlled trial would appear to be the optimal design.

There is also concern as to the early stoppage of this trial following observed benefit from interim analysis. Early termination of clinical trials due to benefit often overestimates overall treatment effect as such trials tend to be on a "random high" with subsequent follow-up data from the same or similar trials showing "regression to the truth" (11-14). It is, however, unlikely that early termination in this trial invalidates the finding of benefit for SM. Firstly, an Independent Data and Safety Monitoring Board was used to decide termination, a staple in modern clinical trials. Secondly, the trial managed to achieve its target sample size, and the termination event number was still over 50% of that planned, thus reducing the risk of stopping on a "random high," a phenomenon often attributable to smaller termination sample sizes. Third, while no predefined statistical termination boundary was reported, the large effect size for the primary endpoint (greater than four times longer TTP for SM vs. placebo) and the associated small p-value (<0.0001) satisfies even the most stringent of interim stoppage boundary rules in today's literature (e.g., the Haybittle-Peto boundary). Lastly, following placebo patient crossover, this trial continued to accrue data and further showed a trend towards both TTP and survival benefit for delayed SM versus immediate SM. This dose-like relationship adds confidence to the interim findings of SM's clinical benefit.

Finally, there is concern as to whether the trial population was representative of the clinical world. While the median maximum dose of IM was 800 mg/day, an unknown number of patients experienced dose escalation of IM up to 1600 mg/day (2)—a dose that is rarely employed in day-to-day practice. It is unclear what effects this would have, if any, on the overall efficacy or safety of SM in the trial under review. It is possible, however, that patients receiving upwards of 1600 mg/day of IM were in a late stage of disease and thus less likely to derive benefit from SM, lowering SM's therapeutic effect size.

The idea that patients can be switched to SM early during the course of disease is supported by observation that significant TTP benefit was found in those patients exhibiting

primary resistance to IM (PD within six months of IM therapy; 17% of total trial population) during subgroup analysis (2). Future trials with a more representative patient population may thus find a greater benefit if SM is offered to patients early in the course of disease progression rather than escalating the maximum dose of IM beyond 800 mg/day, which is not recommended due to toxicity concerns (1).

JOURNAL REFERENCE

The recommendations and evidence have been published in *Current Oncology* (Copyright © 2010 Multimed Inc.; http://www.current-oncology.com/index.php/oncology):

- Younus J, Verma S, Franek J, Coakley N. Sunitinib malate for gastrointestinal stromal tumour in imatinib mesylate-resistant patients: recommendations and evidence. Curr Oncol. 2010 Aug;17(4):4-10.

CONFLICT OF INTEREST

The authors wish to report no conflicts of interest.

ACKNOWLEDGEMENTS

The Sarcoma Disease Site group would like to thank Drs. J. Younus, S. Verma, and J Franek and N Coakley for taking the lead in drafting this systematic review.

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Appendix A: Search strategies.

Medline
1 exp Gastrointestinal Stromal Tumors/
2 GIST.tw.
3 sunitinib malate.tw.
4 Sutent.tw.
5 SU11248.tw.
6 randomi?ed controlled trial.pt.
7 exp Randomized Controlled Trials/
8 phase II.tw.
9 exp clinical trials, phase ii/ or exp clinical trials, phase iii/
10 phase III.tw.
11 1 or 2
12 sunitinib?.tw.
13 or/3-5
14 12 or 13
15 6 or 7
16 or/8-10
17 11 and 14
18 15 or 16
19 17 and 18

EMBASE
1 exp Gastrointestinal Stromal Tumor/
2 GIST.tw.
3 sunitinib malate.tw.
4 sunitinib?.tw.
5 Sutent.tw.
6 SU11248.tw.
7 Randomized Controlled Trial/
8 randomi?ed.tw.
9 Phase 2 Clinical Trial/
10 Phase 3 Clinical Trial/
11 phase II.tw.
12 phase III.tw.
13 1 or 2
14 or/3-6
15 7 or 8
16 or/9-12
17 15 or 16
18 13 and 14
19 17 and 18

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Sunitinib Malate for Gastrointestinal Stromal Tumour (GIST) in Imatinib Mesylate Resistant Patients: EBS Development Methods and External Review Process

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THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review

and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is usually comprised of three sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process*. Summarizes the evidence-based series development process and the results of the formal external review of the draft version of Section 1: Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This EBS was developed by the Sarcoma DSG of the CCO PEBC. The series is a convenient and up-to-date source of the best available evidence on the role of sunitinib malate for GIST developed through a review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario.

Report Approval Panel

This evidence report was reviewed by two members of the PEBC's Report Approval Panel (RAP) with expertise in clinical and methodology issues. A number of issues were brought to light:

1. An a priori statement is needed identifying outcomes of interest.
2. Discussion is needed regarding the choice of placebo as comparator and how IM resistance/intolerance criteria were derived.
3. Discussion is needed regarding the methodological importance of stopping clinical trials early for benefit.
4. Some of the secondary outcomes need to be separated from the key evidence so as to not overshadow the key evidence.
5. Overall, the document reads like a technical report and requires more discuss to put results into context of broader disease management.
6. Discuss the implications of sunitinib malate as first-line therapy.

The Sarcoma DSG received and responded to all comments. A Discussion section was added to address the majority of concerns and provide additional context and commentary. Key evidence was separated from secondary evidence to highlight those outcomes of interest that are considered most important in terms of driving policy. An "Outcomes of Interest" heading was added. Lastly, as no trials have reviewed sunitinib malate as first-line therapy for metastatic GIST, the Sarcoma DSG felt unable to comment (outside of pure speculation) on the use sunitinib malate in this way, and thus no discussion on this topic was included.

External Review by Ontario Clinicians

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of the Recommendations and Evidentiary Base of this EBS and review and approval of the report by the PEBC Report Approval Panel, the Sarcoma DSG circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the Sarcoma DSG.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review March 31, 2009)

QUESTION

Is sunitinib malate (marketed as Sutent) superior to placebo or other intervention for primary outcomes of interest in adult patients with gastrointestinal stromal tumour(s) who have developed resistance or exhibit intolerance to imatinib mesylate?

INTENDED AUDIENCE

This guideline is meant for use by clinicians directly involved in the treatment of the target population.

TARGET POPULATION

Adult patients with unresectable or metastatic/recurrent GIST who have been previously treated with, and subsequently developed resistance or intolerance to IM.

OUTCOMES OF INTEREST

Outcomes of interest include TTP, OS and toxicity. While the impact on OS is the most influential outcome in terms of driving policy, outcomes such as TTP or progression-free survival (PFS) are increasingly valued in oncology trials dealing with metastatic disease. Such outcomes may in fact be the only signals of benefit in randomized trials where event-driven interim analyses lead to the unblinding of treatment arms or the crossover of patients between arms, or where other interventions that might affect post-trial survival are employed. In previous trials examining patients with unresectable/metastatic GIST, TTP has been suggested as an appropriate endpoint. The Sarcoma DSG acknowledges that clinicians, patients, and regulators must increasingly consider surrogates such as TTP to guide practice and inform policy where appropriate.

RECOMMENDATIONS AND KEY EVIDENCE
Recommendations

Sunitinib malate, administered at a dose of 50 mg/day in six-week cycles (four weeks on, two weeks off), is a recommended treatment option in patients with unresectable or metastatic/recurrent GIST who demonstrate:

- **Early progression (within six months) while on imatinib mesylate (as measured by** Response Evaluation Criteria In Solid Tumors **[RECIST] criteria)**

- **Progression following treatment with escalated doses of imatinib mesylate of up to 1600 mg/day (as measured by RECIST criteria)***
- **Intolerance to imatinib**

Treatment should continue in six-week cycles until progression or intolerance. Patients should be encouraged to participate in appropriate clinical trials.

*** The Sarcoma DSG does not advise escalating doses of imatinib mesylate beyond 800 mg/day due to toxicity concerns.**

Key Evidence

- One double-blind, multicentre, randomized controlled trial (RCT) by Demetri et al. (2) examined the use of sunitinib malate in the target population. Results reported here were derived at the time of a first, planned interim analysis:
  - In 312 patients randomized 2:1 (207 SM to 105 placebo), median TTP (primary endpoint) was significantly longer in patients treated with SM than in those treated with placebo at the time of a planned, first interim analysis (27.3 versus [vs.] 6.4 weeks, hazard ratio [HR] 0.33, 95% confidence interval [CI] 0.23-0.47, p<0.0001). Similar HRs in favour of sunitinib malate were reported in stratified analyses and in Cox proportional hazard models when controlling for baseline factors.
  - Patients treated with SM had longer PFS (24.1 vs. 6.0 weeks, HR 0.33, 95% CI 0.24-0.47, p<0.001) and improved OS (HR 0.49, 95% CI 0.29-0.83, p=0.007, absolute difference in weeks not reported) (2).

Additional Evidence

The analysis reported by Demetri et al. (2) above under Key Evidence also included the following results:

- SM therapy induced partial response (PR) in 6.8% of patients and durable stable disease (SD≥22 weeks; deemed clinically significant) in 17.4% vs. 0% PR and 1.9% SD in placebo patients (3). The objective response rate (ORR) was significantly higher in patients treated with SM (7.0% vs. 0%, 95% CI 3.7-11.1%, p=0.006) (2). Four of nine IM-resistant patients achieved PR with sunitinib malate therapy, whereas none of four IM-resistant patients achieved PR with placebo (3).
- There was no difference in quality of life (QOL) as measured by EuroQol Visual Analog Scale (EQ-VAS) scores between the SM therapy arm and placebo over time. A non-significant trend towards higher pain relief response rate was observed for the SM group over placebo in the intention-to-treat (ITT) population (17.4% vs. 9.5%, p=0.064) and in patients who reported pain or analgesic use at baseline (31.0% vs. 17.2%, p=0.052) (3).
- SM therapy was generally well tolerated. The most frequent of all adverse effects (AEs) experienced in greater proportion by patients on SM over placebo were Grade 1/2 leucopenia (52% vs. 5%), neutropenia (43% vs. 4%), and thrombocytopenia (36% vs. 4%). Grade 3 hematological AEs were also reported more frequently in the SM group, including leucopenia (4% vs. 0%), neutropenia (8% vs. 4%), lymphopenia (9% vs. 2%), and thrombocytopenia (4% vs. 0%). P-values were not reported for toxicity comparisons.
- Regarding non-hematological AEs, the incidence of Grade 1-3 fatigue was greater for the SM group in comparison to placebo (34% vs. 22%). Other Grade 3 treatment-related non-hematological AEs that occurred more frequently on

sunitinib malate included hand-foot syndrome (4% vs. 0%), diarrhea (3% vs. 0%), and hypertension (3% vs. 0%). No grade 4 AEs were observed.
- Patients who were intolerant to IM on study entry did not experience recurrence of previous toxic effects when on SM.
- No patients had clinical evidence of congestive heart failure, pancreatitis, or a mean decrease in left ventricular ejection (2).

A presentation from the 2006 American Society of Clinical Oncology (ASCO) annual meetings (3) provides updated data on immediate vs. delayed SM treatment following placebo patient crossover in the trial by Demetri et al. (see Qualifying Statements). The presentation reported that non-significant increases in median TTP (28.9 vs. 24.3 weeks, HR 0.90, 95% CI 0.52-1.54, p=0.691) and in OS (HR 0.76, 95%CI 0.54-1.06, p=0.107) were observed in patients who received immediate SM treatment versus delayed treatment. By the time of TTP and survival analysis, 70% (83/118) of placebo patients had crossed over to SM treatment. Placebo patient crossover did not alter the toxicity profile.

Qualifying Statements

- This review addresses the results of a single trial presented across several publications. The trial was stopped early following a planned interim analysis. Subjects were unblinded and allowed to cross over from placebo to SM. Notwithstanding the ethical considerations that should be taken into account in such settings, there is growing concern in the literature over trials that are stopped prematurely, and clinicians should interpret results of this trial only after understanding the methodological concerns (see Discussion).
- Resistance to IM was defined by progression as denoted by RECIST criteria. Thresholds for progression as bulleted in the above recommendations, for example, early progression (within six months) while on IM, and progression following treatment with escalated doses of IM (up to 1600 mg), were established both according to the entry criteria of the trial under review and based on prior knowledge and standard practice with IM for recurrent/metastatic GIST (see Discussion).
- While the Sarcoma DSG recommends SM for patients with resistance to IM on escalated doses of 1600 mg (as per trial entry criteria), the DSG does not actually recommend escalating IM doses beyond 800 mg because of concerns with toxicity (1).
- In the original trial report by Demetri et al. (2):
  - At the time of documented disease progression, treatment assignments were unblinded. Placebo patients were given the option of switching to SM, while those patients who were already receiving SM were given the opportunity to continue treatment at the investigator's discretion. As a result, and when considering the short follow-up time, the difference in OS between treatment group may have been reduced at the time of the first, planned interim analysis.
  - Study populations were analyzed according to ITT principles (all patients as randomized according to original randomization scheme), modified ITT (all ITT patients with disease progression on IM, and per protocol (all patients who received at least one dose of assigned study treatment). ITT data were reported for all efficacy measures and per protocol for safety.
- In the updated presentation from the 2006 ASCO annual meeting (3):

- Updated analyses included placebo patients who had crossed over to sunitinib malate treatment following the favourable results observed for median TTP at the time of the first, planned interim analysis (as noted above). Thus, any updated analyses reflect immediate versus delayed sunitinib malate treatment and not SM versus placebo as the original trial data reported.
- The delayed treatment arm for updated TTP analyses included only those patients originally randomized to placebo who crossed over to receive SM treatment prior to any disease progression, hence the low sample size (n=24).
- Because the placebo patient crossover altered planned trial methodology, no statistical adjustments for prior interim analyses were necessary for the updated data.

Methods

Targeted Peer Review: During the guideline development process, six targeted peer reviewers from Ontario, Quebec, Manitoba, and British Columbia considered to be clinical and/or methodological experts on the topic were identified by the Sarcoma DSG. Several weeks prior to the completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Two reviewers agreed, and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on February 24, 2009. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Sarcoma DSGC reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. All medical oncologists in the PEBC database who treat sarcoma were contacted by email to inform them of the survey. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on March 12, 2009. The consultation period ended on April 30, 2009. The Sarcoma DSG reviewed the results of the survey.

Results

Targeted Peer Review: Two responses were received from three reviewers. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=2)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
• **Rate the guideline development methods.**				1	1
• **Rate the guideline presentation.**					2

• **Rate the guideline recommendations.**			1	1	
• **Rate the completeness of reporting.**				1	1
• **Does this document provide sufficient information to inform your decisions? If not, what areas are missing?**				1	1
• **Rate the overall quality of the guideline report.**				1	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
• **I would make use of this guideline in my professional decisions.**				1	1
• **I would recommend this guideline for use in practice.**				1	1

- **What are the barriers or enablers to the implementation of this guideline report?**
  - I do not foresee any barriers
  - The design aberrations that might cause funding agencies to be reluctant to pay are discussed well and, I think, persuasively. Cost-effectiveness has been evaluated by a Spanish group that may provide further encouragement.

Summary of Written Comments and Modifications/Actions

The main points contained in the written comments were:

- The guidelines developed here reproduce the efforts of the Canadian guidelines already published in the Canadian journal of gastroenterology. These guidelines put emphasis on this aspect of the therapy for GIST patients.
  Response: No changes were made to the document.
- Several comments were made on the dosing recommendations regarding disease progression and resistance to imatinib.
  Response: The wording of the recommendations was changed to improve clarity.
- I would have included flt-3 inhibition as being important because it does explain some of the toxicities and is the reason behind the unusual dosing schedule.
  Response: We acknowledge this as an area of further research
- The daily dosing of sunitinib is successfully skirted because of the methodology used. However, some comment might be appropriate
  Response: We are recommending dosage per the clinical trial. No changes were made in the document
- Minor typographical errors
  Response: Corrected in the document

Professional Consultation: No responses were received.

Policy Review

A report on Sunitinib for GIST was sent to the Committee to Evaluate Drugs (CED) in October 2007

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Sarcoma DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

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For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

REFERENCES

1. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13:502-12.
2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31.

Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-based Series 11-8 Version 2: Section 3

Sunitinib Malate for Gastrointestinal Stromal Tumour (GIST) in Imatinib Mesylate Resistant Patients

A. Razak, R. Poon, and the Sarcoma Disease Site Group.

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Guideline Summary Review

Review Date: January 15, 2014

The 2009 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2009. In November 2012, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The Sarcoma Disease Site Group (DSG) endorsed the recommendations found in Section 1 (Recommendations and Evidence) in 2014.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

Is sunitinib malate (marketed as Sutent) superior to placebo or other intervention for primary outcomes of interest in adult patients with gastrointestinal stromal tumour(s) who have developed resistance or exhibit intolerance to imatinib mesylate?

Literature Search and New Evidence

The new search (Jan 2008 to October 2013) yielded 1 new full text publication and 1 conference abstract of randomized control trials. An additional search for ongoing studies on clinicaltrials.gov yielded 1 potentially relevant ongoing trial and 1 completed trial with no study results posted. Brief results of these publications are shown in the Document Review Summary and Tool.

Impact on Guidelines and Its Recommendations

The new data supports existing recommendations. Hence, the members of the Sarcoma DSG ENDORSED the 2009 recommendations on Sunitinib Malate for Gastrointestinal Stromal Tumour (GIST) in Imatinib Mesylate Resistant Patients.

Document Summary and Review Tool

Number and title of document under review	#11-8 Sunitinib Malate for Gastrointestinal Stromal Tumour (GIST) in Imatinib Mesylate Resistant Patients
Current Report Date	June 9, 2009
Clinical Expert	Dr. Albiruni Razak
Research Coordinator	Raymond Poon
Assessment Date	November 21, 2012
Approval Date and Review Outcome (once completed)	January 14, 2014 (ENDORSE)

Original Question(s):
Is sunitinib malate (marketed as Sutent) superior to placebo or other intervention for primary outcomes of interest in adult patients with gastrointestinal stromal tumour(s) who have developed resistance or exhibit intolerance to imatinib mesylate?

Target Population:
Adult patients with unresectable or metastatic/recurrent GIST who have been previously treated with, and subsequently developed resistance or intolerance to IM.

Study Section Criteria:
Inclusion Criteria
Articles were eligible for inclusion if they met the following criteria:
· SM as treatment for adult patients (≥15 years of age) with GIST was evaluated in a randomized phase III controlled clinical trial.
· Clinical trial reports were published as full peer-reviewed articles or publicly-available abstracts or presentations.
· Data reported on one or more of the following outcomes: ORR, TTP, SD rate, PFS, OS, toxicity, or QOL.

Exclusion Criteria

Articles were excluded if they were non-randomized phase I or II clinical trials, retrospective studies, editorials, letters, or articles. Any articles published in languages other than English were also excluded as translation capabilities were not available.

Search Details:

2008 to October 3, 2013 (Medline, Embase, ASCO annual meetings, and clinicaltrials.gov)

Brief Summary/Discussion of New Evidence:

Of 205 total hits from Medline and Embase + 30 total hits from ASCO + 11 total hits from clinicaltrials.gov, 2 references representing 1 randomized control trial (final results from the 2006 study by Demetri et al.) and 1 conference abstract were found. One ongoing trial and one completed trial with no study results posted were identified.

Randomized Control Trials						
Interventions	**Population**	**N**	**Median follow up**	**Outcomes**	**Brief results**	**References**
sunitinib vs. placebo	Adult patients with histologically proven GIST for whom prior imatinib treatment had failed due to resistance or intolerance. Median age: sunitinib=57 placebo=55	Sunitinib=243 placebo=118 (103 of whom crossed over to open-label sunitinib)	41.7 months	• OS	• Kaplan-Meier estimates of median OS for the sunitinib arm was 72.7 weeks (95% CI, 61.3-83.0) versus 64.9 weeks (95% CI, 45.7-96.0) for the placebo arm. HR of 0.876 (95% CI, 0.679-1.129; P=0.306). • To correct for the confounding impact on survival of cross-over placebo-treated patients, the RPSFT method was used to calculate a median OS for the placebo arm of 39.0 weeks (95% CI, 28.0-54.1). HR of 0.505 (95% CI, 0.262-1.134; P=0.306).	Demetri et al., 2012 and Schoffski et al., 2008 (conference abstract)
				• TTP	• The median TTP for the sunitinib arm was 26.6 weeks (95% CI, 16.0-32.1) versus 6.4 weeks (95% CI, 4.4-10.0) for the placebo arm. HR of 0.339 (95% CI, 0.244-0.472; P<0.001).	
				• PFS	• The median PFS for the sunitinib arm was 22.9 weeks (95% CI, 10.9-28.0) versus 6.0 weeks (95% CI, 4.4-9.7). HR of 0.347 (95% CI, 0.253-0.475; P<0.001).	
				• ORR	• The ORR for the sunitinib arm was 7% (95% CI, 4-11) versus 0% for the placebo arm. • The ORR for the cross-over patients was 10%.	
				• SD, PD	• The SD and PD rates for the sunitinib arm were 53% and 19%, respectively versus 42% and 37% for the placebo arm.	
				• Toxicity	• No new safety concerns emerged with extended sunitinib exposure (median	

					22 weeks on drug). Similar to the shorter-term sunitinib treatment (median 8 weeks on drug), the most common nonhematologic AEs were Grade 1/2 fatigue (37%), diarrhea (38%), skin discoloration (30%), and nausea (34%); incidences increased slightly with extended sunitinib therapy. ● The frequencies of hematologic laboratory abnormalities were similar to those seen in the shorter-term sunitinib treatment. ● The frequencies of treatment-related hypertension, hand-foot syndrome, and hypothyroidism (Grade 1-4) increased from 12% to 20%, 11% to 17%, and 3% to 13%, respectively with longitudinal exposure. ● During the shorter-term treatment, 4 treatment-related deaths were reported in the sunitinib arm (cardiac arrest, cerebral ischemia, left ventricular failure, and multiorgan failure) and 2 in the placebo arm (cardiac arrest, gastrointestinal hemorrhage). In addition, 4 deaths were reported during open-label sunitinib treatment or follow-up (hepatic encephalopathy, hepatic failure, melena, and pneumonia).	

Ongoing Randomized Control Trials
Retrieved from www.clinicaltrials.gov

Interventions	Official title	Status	Protocol ID	Estimated primary completion date	Last updated
masitinib vs. sunitinib	A Prospective, Mulitcenter, Randomized, Open-label, Active-controlled, Two-parallel Groups, Phase 3 Study to Compare the Efficacy and Safety of Masitinib to Sunitinib in Patients With Gastrointestinal Stromal Tumor After Progression With Imatinib at 400mg as First Line Treatment.	Recruiting	NCT01694277	January 2015	August 13, 2013
sunitinib malate vs. placebo	A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of SU011248 in the Treatment of Patients With Imatinib Mesylate (Gleevec™, Glivec®)-Resistant or Intolerant Malignant Gastrointestinal Stromal	Completed, no study results posted	NCT00085618	November 2008	December 13, 2009

	Tumor.				

Abbreviations: OS=overall survival; CI=confidence interval; RPSFT=rank-preserving structural failure time; HR=hazard ratio; TTP=time to tumor progression; PFS=progression-free survival; ORR=objective response rate; SD=stable disease; PD=progressive disease; AEs=adverse events

Clinical Expert Interest Declaration:

None

Instructions. For each document, please respond YES or NO to all the questions below. Provide an explanation of each answer as necessary.

1. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?	No
2. On initial review, a. Does the newly identified evidence support the existing recommendations? b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?	Yes to both question 2a and 2b
3. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	No
4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?	Yes

Review Outcome	ENDORSE
DSG/GDG Approval Date	January 14, 2014
DSG/GDG Commentary	Not applicable

New References Identified (alphabetic order):

1. Demetri GD, Garrett CR, Schoffski P, Shah MH, Verweij J, Leyvraz S, et al. Complete longitudinal analyses of the randomized, placebo-controlled, phase III trial of sunitinib in patients with gastrointestinal stromal tumor following imatinib failure. Clinical Cancer Research. 2012;18(11):3170-9.
2. Schoffski P, Huang X, Casali PG, Garrett CR, Blackstein ME, Shah MH, et al. Phase III trial of sunitinib (SU) in imatinib (IM)-Resistant/intolerant GIST with novel statistical analysis of long-Term survival to account for crossover. Annals of Oncology. 2008;19 (S8):viii266.

Literature Search Strategy:

Medline

1. exp Gastrointestinal Stromal Tumors/
2. GIST.tw. OR Gastrointestinal Stromal Tumo?r$.tw.
3. 1 OR 2
4. sunitinib$.tw.
5. Sutent.tw.
6. SU11248.tw.
7. OR/ 4-6
8. exp randomized controlled trials as topic/ OR exp clinical trials, phase III as topic/ OR exp clinical trials, phase IV as topic/
9. (randomized controlled trial OR clinical trial, phase III OR clinical trial, phase IV).pt.
10. random allocation/ OR double blind method/ OR single blind method/
11. (randomi$ control$ trial? OR rct or phase III OR phase IV OR phase 3 OR phase 4).tw.
12. OR/ 8-11
13. ((singl$ OR doubl$ OR treb$ OR tripl$) adj (blind$3 or mask$3 or dummy)).tw.
14. placebos/
15. (placebo? OR random allocation OR randomly allocated OR allocated randomly).tw.
16. (allocated adj2 random).tw.
17. OR/ 13-16
18. 12 OR 17
19. 3 AND 7
20. 18 AND 19
21. (comment OR letter OR editorial OR note OR erratum OR short survey OR news OR newspaper article OR patient education handout OR case report OR historical article).pt.
22. 20 NOT 21
23. limit 22 to English
24. Animal/
25. Human/
26. 24 Not 25
27. 23 Not 26
28. (2008$ OR 2009$ OR 2010$ OR 2011$ OR 2012$ OR 2013$).ed.
29. 27 AND 28

Embase
1. exp Gastrointestinal Stromal Tumors/
2. GIST.tw. OR Gastrointestinal Stromal Tumo?r$.tw.
3. 1 OR 2
4. sunitinib$.tw.
5. Sutent.tw.
6. SU11248.tw.
7. OR/ 4-6
8. exp randomized controlled trial/ OR exp phase 3 clinical trial/ OR exp phase 4 clinical trial/
9. randomization/ OR single blind procedure/ OR double blind procedure/
10. (randomi$ control$ trial? OR rct or phase III OR phase IV OR phase 3 OR phase 4).tw.
11. OR/ 8-10
12. ((singl$ OR doubl$ OR treb$ OR tripl$) adj (blind$3 or mask$3 or dummy)).tw.
13. placebos/
14. (placebo? OR random allocation OR randomly allocated OR allocated randomly).tw.
15. (allocated adj2 random).tw.
16. OR/ 12-15
17. 11 OR 16
18. 3 AND 7
19. 17 AND 18
20. (editorial OR note OR letter OR erratum OR short survey).pt. OR abstract report/ OR letter/ OR case study/
21. 19 NOT 20
22. limit 21 to English
23. Animal/
24. Human/
25. 23 Not 24
26. 22 Not 25
27. (2008$ OR 2009$ OR 2010$ OR 2011$ OR 2012$ OR 2013$).dd.
28. 26 AND 27

ASCO Meeting Abstracts
Searched http://www.ascopubs.org/serach with keywords: “sunitinib” AND “gastrointestinal stromal tumor”.

Clinicaltrials.gov
Searched http://clinicaltrials.gov/ct2/search/advanced with keywords: “sunitinib” AND “gastrointestinal stromal tumor”. Filter was used to limit results to Phase 3 trials.

OUTCOMES DEFINITION

1. **ARCHIVED** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website, each page is watermarked with the word "ARCHIVED".

2. **ENDORSED** – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DELAY –** A delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.

4. **UPDATE** – An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.