Technology Assessment

Technology Assessment Program

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REPORT ON THE RELATIVE EFFICACY OF ORAL CANCER THERAPY FOR MEDICARE BENEFICIARIES VERSUS CURRENTLY COVERED THERAPY: PART 2, IMATINIB FOR GASTROINTESTINAL STROMAL TUMORS (GIST)

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Introduction

Policy Context of the Current Technology Assessment

Section 641 of the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) calls for a demonstration that would pay for drugs and biologicals that are prescribed as replacements for drugs currently covered under Medicare Part B. The demonstration project will be national in scope and will be limited to 50,000 beneficiaries or $500,000,000 in funding, whichever comes first. Forty percent of the funding for this demonstration will be reserved for oral anti-neoplastic drugs.

CMS has requested an assessment of the efficacy of selected oral cancer therapies included in the demonstration relative to drugs currently covered under Medicare Part B. This assessment will provide information that will be used to evaluate the likely effects of the demonstration on patient outcomes and may also provide underlying information to be used for cost-effectiveness analyses that will be completed by CMS.

The scope of the assessment will be limited to the following demonstration drugs and conditions:

- Imatinib for treatment of chronic myeloid leukemia;
- Imatinib for treatment of gastrointestinal stromal cancer;
- Gefitinib for treatment of non-small cell lung cancer; and
- Thalidomide for treatment of multiple myeloma.

This report is responsive to the second item: an assessment of imatinib for the treatment of gastrointestinal stromal tumors (GISTs).

Clinical Context of the Current Technology Assessment

Although relatively rare, GISTs represent the largest subset of mesenchymal tumors of the gastrointestinal (GI) tract and about 5 percent of all sarcomas.[1, 2] They originate in the stroma, the connective tissue that supports the organs involved in digestion. GISTs are now known to be derived from muscle-like nerve cells called the Interstitial Cells of Cajal, which coordinate the automatic movements of the GI tract. During the last three decades there has been considerable debate about GIST's cells of origin, nomenclature, diagnosis, and prognosis. Many cases have not shown up in cancer registries, have been misclassified as other cancers, or defined as benign.[1, 3] For this reason, the exact incidence of GIST is unknown, but is approximated at 5,000 to 10,000 cases in the U.S. annually.[4] Two recent studies from Scandinavia measure the incidence somewhat lower at 1.1 to 1.4 per 100,000.[26,94]

GISTs occur predominantly in middle and older aged individuals; the median age at diagnosis is about 60 years.[2] They affect men and women equally.[2] The majority (70 percent) of tumors

occur in the stomach, with 20-30 percent in the small bowel and < 10 percent elsewhere in the GI tract.[1] GISTs vary greatly in size with tumor sizes ranging from 1 to over 20 centimeters (cm).[1]

Surgical resection is the primary therapy of choice for all localized gastrointestinal stromal cell lesions at the time of initial presentation.[3, 5] The goal is to completely remove the tumor. GISTs are now classified based on a spectrum of risk, from very low-risk disease (unlikely to recur or metastasize) to high risk disease which would commonly recur and metastasize with life-threatening consequences; the rapidity and timing of tumor progression and metastasis is highly variable.[6] Five-year survival rates after complete resection for all patients overall with primary GIST and without accounting for risk stratification are 48-65 percent.[5] The ability to resect the tumor is an important prognostic determinant (Table 1). In a multivariate analysis of 200 cases of GIST referred to a major cancer center, important negative predictors of survival included male gender (relative risk (RR) 1.6, confidence interval (CI) 1.0-2.6), size > 5 cm (5-10 cm (RR 2.8, CI 1.3-6.2), > 10 cm (RR 4.4, CI 2.0-9.8)), and incomplete resection of the tumor (RR 3.9, CI 2.4-6.2).[2] In this series, over 80 percent were > 5 cm at the time of diagnosis. Other single institution studies report similar findings.[7]

When complete resection was possible, local recurrence occurred within 2 years in approximately 10 percent of individuals whose primary tumor has been completely resected, metastatic recurrence in approximately 15 percent, and synchronous local and metastatic in 5 percent.[2] Complete resection is not possible in up to 40 percent of cases.[2, 7, 8]

Pathology is important for differentiating GISTs from other tumors and prognosis (Table 1). Under the light microscope GISTs are composed of spindle-shaped or epithelioid appearing cells; the cells are usually more numerous with less eosinophilic cytoplasm than leiomyomas.[9, 10] The immunohistochemical staining pattern is critical for diagnosis. Immunohistochemistry is the use of antibodies or antisera to detect a specific marker within a pathological specimen; when a tumor reacts with an immunohistochemical stain, then it is termed "positive" for that antigen and the tumor is recognized as producing the specific marker of interest. Approximately 70 percent of GISTs are positive for CD34, 20-30 percent are positive for smooth muscle actin (SMA), 10 percent are positive for S100 protein, and 5 percent are positive for desmin.[10] CD117, the antigen that corresponds with the c-kit proto-oncogene product, is positive in over 90 percent of GISTs.[1, 11-15] Other tumors are CD117 positive but most of these do not occur in the GI tract and are not part of the differential for GIST.[1] The WHO classification of gastrointestinal tumors indicates that the term GIST should be reserved for CD117 positive tumors, but the current literature accepts the concept that there are some CD117 negative GISTs.[16]

In GIST a specific change or mutation in DNA at the point of the c-kit proto-oncogene causes a cellular enzyme known as KIT to be switched "on" all the time. These activating mutations are most commonly localized on exon 11 (57-71 percent), exon 9, or exon 13 of the KIT gene.[1] KIT is a tyrosine kinase enzyme responsible for sending growth and survival signals inside the cell. If it is "on", the cell stays alive and grows or proliferates. The overactive, uncontrolled mutant KIT enzyme triggers the malignant growth of GIST tumor cells. GISTs with mutant KIT are more likely to be aggressive tumors characterized by more frequent recurrence and a higher associated mortality rate. For example, in a Japanese study of 124 patients with GIST, 89 percent were KIT positive, 57 percent of c-kit mutations were missense mutations on exon 11, and the patients with mutation-positive GISTs showed more frequent recurrences ($p < 0.001$) and higher mortality ($p < 0.001$) than did those with mutation-negative GISTs.[12] Other groups have

observed similar findings, but this was not consistent across all studies.[17-19] Exon 9 mutations have also been associated with more aggressive tumor characteristics, including larger tumor size and extra-gastric locations.[20, 21] CD117 negative GISTs may have a mutation in the platelet-derived growth factor receptor (PDGFR) gene that produces a similar tyrosine kinase; this does not appear to be prognostically significant.[15, 22, 23]

Pathological characteristics such as sites of origin outside of the stomach, large size, nuclear atypia, high mitotic rate, and mucosal invasion are also associated with the ability of a cancer to spread.[1, 15, 24] For example, in one series of 1,074 cases of GIST, mitotic activity predicted survival such that only 3 percent of patients with low mitotic activity (≤ 5/50 HPFs) died, as opposed to 46 percent with high mitotic activity (> 5/50 HPFs, $p < 0.0001$).[15] Larger tumor size and location (e.g., stomach fundus and gastroesophogeal junction) undermine tumor respectability and hence are negative predictors of prognosis.[5, 15] Taken together, tumors with high mitotic activity and larger size are most aggressive, such that 16 percent of patients with small mitotically active tumors (2-5 cm, > 5/50 HPFs) died, as opposed to 49 percent with mitotically active 5-10 cm tumors, and 86 percent with mitotically active > 10 cm tumors.[15] These two factors (mitotic count and tumor size) were used by and NIH-convened workshop to define the risk of aggressive behavior in GISTS [25]; the validity of this scheme was demonstrated in a subsequent population-based study [26]

Recent reviews suggest that scientifically advanced genetic markers, including DNA-copy number changes, telomerase activity, KIT mutation status, and KIT mutation type (point vs. deletion) may be useful in more accurately identifying tumors with malignant potential,[13, 15, 24] however, the most important utility of KIT and PDGFR genotyping may be in prediction of drug effects using kinase inhibitors such as imatinib.[27]

Table 1: Summary of major tumor characteristics reported to predict poor survival

Most consistently reported characteristics
Size > 5 cm
Inability to completely resect the tumor
Exon 11 and 9 KIT mutations
High mitotic rate
Less consistently reported characteristics
Site of origin
Nuclear atypia
Mucosal invasion
DNA copy number changes
Telomerase activity
KIT point vs. deletion mutations

In the pre-imatinib era, the usual course after complete resection has been vigilant watchful waiting.[3, 5] Adjuvant chemotherapy after surgery designed to reduce the chance of GIST recurrence has been moderately successful.[28, 29] In a 1997 meta-analysis of randomized trials of doxorubicin-containing chemotherapy, adjuvant chemotherapy improved recurrence-free survival (hazard ratio (HR) 0.75, CI 0.64-0.87, $p = 0.0001$) but not overall survival (HR 0.89, CI 0.76-1.03, $p = 0.12$).[28] Recurrent disease may be treated with repeat surgery when possible.[2] The prognosis for unresectable or metastatic GIST has historically been poor, with 5-year survival rates estimated to be lower than 5 percent.[1, 5] Historically unresectable or metastatic

disease was treated with radiotherapy, single-agent doxorubicin, single-agent ifosfamide, and combination chemotherapy including these agents although none of these have clinically meaningful anti-tumor activity.[1] Management of advanced tumor and improvements in survival with these interventions has been poor.[16] Hence, the usual plan of care in the pre-imatinib era was resection whenever possible with or without adjuvant therapy, surveillance for recurrence and metastatic disease, followed by chemotherapy for advanced disease generally with doxorubicin- and/or ifosfamide-based regimens and possibly radiotherapy for selected cases.

The UK National Institute for Clinical Excellence (NICE) conducted a systematic review of non-imatinib treatments for advanced GIST.[16] The interventions reviewed were heterogeneous including novel chemotherapeutics and/or standard sarcoma chemotherapy regimens. The studies included patients with GISTs, non-specific soft tissue sarcomas, GI sarcomas, and leiomyosarcomas. Overall survival was 72 percent (18-100 percent) at 1 year, 40 percent (30-66 percent) at 2 years, and 16 percent (0-40 percent) at 3 years. A total of 13 of 258 patients (5 percent) achieved a partial response, while 64 (24 percent) had stable disease. NICE concluded that the heterogeneity of treatments, small numbers of patients involved, diagnostic difficulties, and uncontrolled study designs made it difficult to interpret these studies as a true historical baseline for imatinib.

The National Cancer Institute (NCI) health professionals guidelines at www.cancer.gov are a frequent resource for U.S. oncologists.[30] Expert reviewers of this systematic summary of the literature highlight that this NCI guideline is very outdated in terms of recommendations for the management of GIST. In recommending chemotherapeutics, this site does not specifically differentiate recurrent or metastatic advanced GIST from other advanced soft-tissue sarcomas. According to this summary, which is related to soft-tissue sarcomas overall and is not focused on GIST, only doxorubicin and ifosfamide show response rates > 20 percent for advanced disease when used as single agents.

> *Doxorubicin:* Single-agent doxorubicin response rates vary from 15-34 percent with median 26 percent; the majority of these responses are partial responses only.[31] In 1999, Bramwell et al. of Program in Evidence-based Care of Cancer Care Ontario conducted a systematic review of randomized trials and developed an evidence-based guideline on doxorubicin for advanced soft-tissue sarcomas (available at www.guidelines.gov). In this guideline, single-agent doxorubicin response rates ranged from 16-30 percent; meta-analysis did not show a significant response benefit for single-agent doxorubicin nor combination chemotherapy containing doxorubicin.[32] Toxicity data were also reviewed in this document. This summary is related to soft-tissue sarcomas overall and is not focused on GIST.
>
> *Ifosfamide:* In a widely-cited review of chemotherapy for advanced soft tissue sarcomas, single-agent ifosfamide response rates vary from 7-38 percent with median 26 percent in patients with previously treated sarcomas.[31] Similar estimates were cited by other reviewers.[33] Approximately 24 percent of patients who have progressed after doxorubicin can respond to ifosfamide.[34] There is a clear dose–response relationship with single agent ifosfamide.[35, 36] In sequential studies, one group reported response rates of 10 percent at 6 g/m^2, 14 percent at 8 g/m^2 , 21 percent at 10 g/m^2, and 29 percent at 14

g/m^2.[36] Again, this summary is related to soft-tissue sarcomas overall and is not focused on GIST.

Combination of these drugs may be more effective, especially for younger patients who can tolerate this program; a randomized trial of 340 patients with advanced sarcoma showed a higher response rate (32 percent vs. 17 percent, $p < 0.002$) and longer time-to-progression (TTP, 6 vs. 4 months, $p < 0.02$) for doxorubicin, dacarbazine, ifosfamide, and mesna (MAID) vs. doxorubicin and dacarbazine alone.[37] According to the NCI website, sequential use of doxorubicin followed by ifosfamide or other drugs with each subsequent recurrence is still frequently preferred for older patients.[30] GIST is not specified within these trials, and given the difficulty with diagnosis of GIST during the period during which these trials were conducted any specific referrals to GIST outcomes are suspect.

Across this body of work representing the comparative efficacy for single and multi-agent chemotherapy for GIST, there are repeated problems with reliability of the information. Nearly all of this work pre-dated the ability to distinguish GIST from other soft tissue sarcomas. GIST is likely to be more chemoresistant than other soft tissue sarcomas,[38 39] and therefore the estimated efficacy of doxorubicin- and/or ifosfamide-based chemotherapy for GIST is likely to be less than the overall efficacy for soft tissue sarcomas reported here. The inclusion of GIST in the original studies about chemotherapy for soft tissue sarcomas may in fact reduce the estimated efficacy of doxorubicin- and/or ifosfamide-based chemotherapy of other non-GIST soft tissue sarcomas.

The Technology

Both the KIT tyrosine kinase and Platelet-Derived Growth Factor Receptor Alpha (PDGFRA) targets of imatinib are receptor tyrosine kinase proteins that are located within the plasma membrane on the surface of both normal cells as well as the cells of GIST.[40, 41] In the normal state, KIT is stimulated by stem cell factor (SCF) sending a signal inside the cells that tells them to grow only as needed, while the PDGFRA is stimulated by platelet derived growth factor (PDGF) dimers acting as a ligand for the receptor. As described previously, in the vast majority (95 percent) of GIST lesions, the DNA of the c-kit proto-oncogene is mutated and the KIT and PDGFRA proteins are continuously switched "on" in the absence of regulating ligands. This continuous "on" state is called constitutive KIT or PDGFRA protein kinase activity. This constant signal tells the cancerous cells to keep growing and is a critical contributing factor to the development and maintenance of the malignancy.

Imatinib (STI-571, trade name Gleevec (USA) or Glivec (non-US)) is a derivative of 2-phenylaminopyrimidine.[16] Imatinib is a tyrosine kinase inhibitor that targets several different tumor proteins, including the KIT and PDGFRA proteins that are the major etiologic factors of GIST.[40] It is a competitive inhibitor of the tyrosine kinases associated with PDGFRA, the Abelson (ABL) protein, and the KIT protein. Imatinib works by blocking, or turning off, the message from these relevant target signaling proteins, so that the cancerous cells stop growing.

Imatinib is available as an oral medication and is usually taken once a day at a recommended dose of either 400 milligrams/day (mg/d) or 600 mg/d.[42, 43] Imatinib should be administered with a meal and a large glass of water. Doses over 600 mg/d should be administered in divided doses, e.g., 400 mg twice daily. Tablets are available in 100 mg and 400 mg forms. Treatment can be continued as long as there is no unacceptable toxicity.

Imatinib was first used in patients with chronic myelogenous leukemia (CML). It was Food and Drug Administration (FDA) approved for the treatment of patients with KIT (CD117) positive unresectable and/or metastatic malignant GIST on February 1, 2001.[42, 43]

Scope and Key Questions

The key questions for this review were developed with experts in the field of oncology, health economics, and health policy. The key questions are as follows:

1. In patients with GIST, what is the effect of imatinib compared to doxorubicin and ifosfamide on overall survival, disease free survival, time to progression, CR, PR, and quality of life?

2. In patients with GIST, what is the effect of imatinib compared to doxorubicin (Adriamycin) and ifosfamide on adverse effects, tolerability, and compliance with treatment?

3. What patient or tumor characteristics distinguish treatment responders from non-responders and have potential to be used to target therapy?

Methods

Search Strategy

The search strategy was constructed by combining three concepts: 1) the intervention imatinib; 2) the disease gastrointestinal stromal tumor; and 3) prospective clinical trials. To identify the intervention concept, since these new drugs lack a specific term in the MeSH lexicon, we used text word searching for the following text strings: imatinib or gleevec or glivec or STI571. The disease concept was implemented using the text word searching for *gist* or adjacent text strings for gastro$ within two words of stromal adjacent to (tumo$ or cancer$). This is designed to detect various spellings such as *gastrointestinal stromal tumor* or *gastrointestinal stromal cancer* or *gastro-intestinal stromal cancer, etc*. A published strategy, validated for finding randomized controlled trials (RCTs), was used to identify prospective clinical trials. This strategy is designed to find all prospective clinical trials (maximize sensitivity), rather than to eliminate non-randomized trials (maximize specificity), and so is appropriate for this study's goal of finding phase II and III prospective clinical trials. Finally, the three concepts were combined (Boolean "or"). The strategy was executed in MEDLINE (1966 through September 2004, updated February 2005) and limited to articles published in the English language. The exact text of the OVID MEDLINE versions of the search strategy is provided in Appendix A.

Supplemental searches were conducted in International Pharmaceutical Abstracts, *The Cochrane Library* (Central Register of Controlled Trials (CENTRAL) and Health Technology Assessment [22] database), American Society of Hematology 2004 annual meeting abstracts database, and in the American Society of Clinical Oncology 2004 annual meeting abstracts database. References lists of identified studies and relevant systematic reviews and meta-analyses were hand-checked. Additional articles not indexed in the major bibliographies by September 2004 were identified through ongoing searches and discussions with field experts and monitoring new sources.

Selection Criteria

Each citation identified from the search strategies was evaluated according to the following selection criteria. Evaluations were performed by the authors.

Inclusion criteria were as follows:

Patients	Patients with unresectable or metastatic GIST
Interventions	Imatinib (Gleevac™ or Glivec™ or (STI571))
Comparators	Any

Study designs:

- *For **efficacy** questions*: Prospective clinical trials; may be phase II uncontrolled, or phase III randomized controlled trials.

- *For studies of **adverse effects**:* May be retrospective or prospective case series, cohort studies, or clinical trials, provided the number of patients treated (at risk for adverse effects) as well as the number with adverse effects can be ascertained.

- *For studies of **predictors** of response:* May be retrospective or prospective case series, cohort studies, case-control studies, or clinical trials, provided the response can be ascertained for patients with and without the predictor.

Outcomes:

- *For **efficacy** questions*: Survival, disease-free survival, tumor response, and quality of life (QOL). Tumor response was defined according to Table 2.

- *For studies of **adverse effects**:* Adverse effects, tolerability, and compliance with treatment.

- *For studies of **predictors** of response:* Predictive value of patient or tumor characteristics that are associated with clinically important differences in treatment response that are:
  1) related to the mechanism of action of the drug (i.e., molecular target); and
  2) candidates for diagnostic testing (even if not commercially or clinically available currently (e.g., Polymerase Chain Reaction)).

Table 2. Definitions of tumor response terminology relevant to GIST[†]

Complete response (CR)	The disappearance of all signs of cancer in response to treatment. This does not always mean the cancer has been cured
Partial response (PR)	A decrease in the size of a tumor, or in the extent of cancer in the body, in response to treatment
Response rate (RR)	The percentage of patients whose cancer shrinks or disappears after treatment. RR = CR + PR
Stable disease (SD)	Cancer that is neither decreasing nor increasing in extent or severity
Progressive disease (PD)	Cancer that is growing, spreading, or getting worse
RECIST criteria	RECIST criteria are a voluntary, international standard for measuring tumor response based on measurable disease (i.e., the presence of at least one measurable lesion). RECIST criteria offer a simplified, conservative, extraction of imaging data and presume that linear measures are an adequate substitute for 2-D methods. There are four response categories: CR = disappearance of all target lesions PR = 30% decrease in the sum of the longest diameter of target lesions PD = 20% increase in the sum of the longest diameter of target lesions SD = small changes that do not meet above criteria
SWOG criteria‡	SWOG criteria are based entirely on CT or MRI CR = disappearance of all disease that could be measured and evaluated PR = ≥ 50 percent decrease in the sum of the products of the perpendicular diameters of all measurable lesions, the absence of progression, and the absence of new lesions PD = ≥ 50 percent increase or an increase of 10 cm^2 (whichever was smaller) in the sum of the products of the perpendicular diameters of all measurable lesions, worsening of a lesion that could be evaluated, the reappearance of and lesion or the presence of a new lesion SD = a response that did not qualify as a complete response, a partial response or disease progression
Overall survival	The percentage of subjects in a study who have survived for a defined period of time. Usually reported as time since diagnosis or treatment. Also called the survival rate
Time to progression	A measure of time after a disease is diagnosed (or treated) until the disease starts to get worse
Progression-free survival	One type of measurement that can be used in a clinical study or trial to help determine whether a new treatment is effective. It refers to the probability that a patient will remain alive, without the disease getting worse
Disease-free survival	Length of time after treatment during which no cancer is found. Can be reported for an individual patient or for a study population
Event-free survival*	Length of time after treatment that a participant in a clinical study remains free of pre-defined events. Events are defined by the study and can include adverse treatment effects, tumor recurrence/progression, or survival
Survival rate	The percentage of people in a study or treatment group who are alive for a given period of time after diagnosis. This is commonly expressed as 5-

year survival

†Except as noted, these definitions were quoted from the NCI's www.cancer.gov Web site.

*Definition derived from http://www.intelihealth.com/IH/ihtPrint/WSIHW000/8096/8241/347567.html?d=dmtContent&hide=t&k=basePrint#efsurvival.

‡Defintion from [44]

Data Abstraction

The following data were abstracted from included studies: study design, population characteristics (including sex, age, and diagnosis), eligibility and exclusion criteria, interventions (dose and duration), outcomes assessed and results for each outcome.

We developed data collection forms in Excel (Microsoft; Redmond, WA) and summarized the data in evidence tables formatted like those in a 2003 report from NICE.[16]

Quality Assessment

We assessed the quality of included studies by evaluating elements of internal validity (e.g., randomization and allocation concealment; similarity of compared groups at baseline; specification of eligibility criteria; blinding of assessors, care providers, and patients) and external validity (e.g., description of the patient population, similarity to the target population of the report, use of highly selective criteria).

We used as a framework the quality assessment criteria from NICE.[16] These are displayed in Appendix B. They provide specific criteria for the range of study designs used in this report including experimental studies, cohort studies, case-control studies, and case series.

Point scores were allocated by assigning one point for each quality category. There were a total of 6 possible categories. Quality ratings of "yes" to a quality criteria were assigned 1 point; no and unknown were both assigned 0 points. The last category, adequate description of subseries, was not applicable to all studies. Hence, the total possible quality points were 5 or 6 depending upon the applicability of the subseries category. High quality studies were those with $\geq 3/5$ or 4/6 points.

Abstract quality was not scored.

Data Synthesis

In addition to the data abstraction and quality analysis, a narrative description of study findings was prepared. Further quantitative analyses were considered, but the available data were not adequate to support these.

Results

The search strategy yielded 88 articles. The selection process is described below:

Identified by search strategy
(N = 88)
|------ Excluded based on review of abstract
| (N = 54)
|
Included based on review of abstract
(N = 34)
|
|------ Excluded based on full-text review
| (N = 11)
| 4 not phase II-III for efficacy
| 3 no primary or original data (review article)
| 1 wrong disease
| 3 wrong outcome
|
Included in full-text review and evidence tables
(N = 23)

The 23 included reports comprised 16 full reports and 7 abstract-only publications (Table 3). Study designs included two phase III controlled clinical trials (ongoing, three abstract reports), five phase II uncontrolled clinical trials (four trials in eight full reports plus one trial in one abstract), and eight studies of other designs. Four of these studies with other designs evaluated the role of surgery plus imatinib and four were investigating the role of imaging techniques in predicting GIST outcomes. There were several sub-studies of the phase II trials assessing predictors of GIST outcomes–one assessing radiological predictors, four of tumor characteristics, and two of other clinical predictors. All of the adverse events data were derived from the four phase II clinical trials that were published in full reports.

Quality of the studies varied by outcome category. All of the main imatinib efficacy studies published in full were of high quality. Only one of the four imatinib plus surgery studies was of high quality. Two of the four molecular predictor studies were of high quality, with one low quality study and one abstract. Two of five radiological predictor studies were of high quality, with one low quality study and two abstracts. With the exception of the one abstract, all of the studies reported other types of predictors were of high quality. In summary, study quality was generally high, with surgical and radiological studies being the most suspect.

Table 3. Details of included studies

Study #	First Author, Year	Phase	Report type	Quality	Comments
Imatinib efficacy studies					
1	van Oosterom, 2001[6]	I/II	Full report	3/5	Main results
1	van Oosterom, 2002[45]	III	Full report	3/5	Followup efficacy data for van Oosterom et al. 2001
2	Demetri, 2002[46]	II	Full report	5/5	Main results
2	Dagher 2002[43]	II	Full report	5/5	FDA approval summary with review of Demetri et al. 2002 data
2	Heinrich, 2003[47]	II	Full report	6/6	Follow up efficacy data for Demetri et al. 2002
3	Verweij, 2003[48]	II	Full report	6/6	Main results
4	Verweij, 2004[49]	III	Full report	6/6	Main results
4	Zalcberg, 2004[50]	II	Abstract	Unk	Followup efficacy data for Verweij et al. 2004
5	Casali, 2004[51]	II	Abstract	Unk	Early results of phase II trial
6	Blay, 2004[52]	III	Abstract	Unk	Early results of phase III trial
7	Rankin, 2004[53]	III	Abstract	Unk	Early results of phase III trial
7	Patel, 2003[54]	III	Abstract (published 2003 abstract plus commentary)	Unk	Early results of Rankin et al. 2004 Phase III trial
Imatinib plus surgery efficacy studies					
8	Bumming, 2003[55]	II	Full report	4/6	Main results
9	Rutkowski, 2003[56]	Retro	Full report	1/6	Main results
10	Scaife, 2003[57]	Retro	Full report	2/5	Main results
11	Wu, 2003[58]	Retro	Full report	1/6	Main results
Adverse events/harm					
1	van Oosterom, 2001[6]	I/II	Full report	3/5	Adverse event data reported within main results full report
1	van Oosterom, 2002[45]	III	Full report	3/5	Follow up adverse event data for van Oosterom et al. 2001
2	Demetri, 2002[46]	II	Full report	5/5	Adverse event data reported within main results full report
2	Dagher 2002[43]	II	Full report	5/5	FDA approval summary with review of Demetri et al. 2002 data
3	Verweij, 2003[48]	II	Full report	6/6	Adverse event data reported within main results full report
4	Verweij, 2004[49]	III	Full report	6/6	Adverse event data reported within main results full report

Study #	First Author, Year	Phase	Report type	Quality	Comments
Predictors – tumor characteristics					
1	Debiec-Rychter, 2004[59]	I/II	Full report	6/6	Molecular predictors, sub-study of van Oosterom et al. 2001
2	Frolov, 2003[60]	II	Full report	1/6	Molecular predictors, sub-study of Demetri et al. 2002
2	Heinrich, 2003[47]	II	Full report	6/6	Molecular predictors, sub-study of Demetri et al. 2002
3	Verweij, 2003[48]	II	Full report	6/6	Other predictors reported within main results full report
Predictors – radiological findings					
1	Stroobants, 2003[61]	I/II	Full report	4/6	Radiological predictors, sub-study of van Oosterom et al. 2001
12	Antoch, 2004[62]	Pros	Full report	5/5	Radiological predictors study
13	Gayed, 2004[63]	Pros	Full report	1/5	Radiological predictors study
14	Di Giorgi, 2004[64]	Pros	Abstract	Unk	Radiological predictors study
15	Laussau, 2004[65]	Pros	Abstract	Unk	Radiological predictors study
Predictors – other clinical factors					
2	Heinrich, 2003[47]	II	Full report	6/6	Other predictors, sub-study of Demetri et al. 2002
4	Verweij, 2004[49]	III	Full report	6/6	Other predictors reported within main results full report

Abbreviations: Retro = retrospective; Unk = unknown; Pros = prospective

Efficacy

Imatinib Alone for Advanced GIST

There are four completed high quality studies of imatinib alone for the management of unresectable or metastatic CD117-positive GIST (Table 4) involving a total of 1156 patients with GIST. The patient populations were nearly identical except for the studies by van Oosterom et al. and Verweij et al. (2001) which included some patients with non-GIST soft tissue sarcomas (STS). When described, 83-98 percent of patients had prior surgery, 33-71 percent of patients had prior chemotherapy, and 8-24 percent of patients had prior radiotherapy. The average age was 55 with a range of 18-83; 62 percent were male.

The completed trials comprise several different designs. The first is a mixed phase design with a dose escalation phase from 400 mg to 1000 mg and phase III follow through at 800 mg (total N = 40).[6, 45] The second is a randomized phase II with patients randomized to 400 or 600 mg daily (total N = 147).[43, 46, 47] The third is a standard phase II design evaluating efficacy of 800 mg daily (N = 50).[48] The fourth is randomized phase III with patients randomized to 400 or 800 mg daily (total N = 946).[49] Followup lasted 9-25 months. There is one incomplete phase II trial reported in abstract form only.[51] This trial appears to be a standard phase II with 135 patients (mean age 65, 70 percent male) receiving an unspecified dose of imatinib.

Tumor response was the most consistent outcome reported. In the completed phase II and phase III studies, complete response (CR) rates ranged from 0-6 percent, partial response (PR) rates ranged from 45-67 percent, and stable disease (SD) rates ranged from 19-47 percent. Overall response (CR + PR) was 49-71 percent.

Overall survival (OS), disease-free survival (DFS), event-free survival (EFS), and progression-free survival (PFS) were variably reported. Verweij et al. (2004) had the longest median follow up (760 days), and reported 1 year OS as 85 percent for either the 400 mg/d or 800 mg/d doses and 2 year OS as 69 percent for the 400 mg/d dose and 74 percent for the 800 mg/d dose (p not significant).[49] Two-year PFS on that study was 44 percent for the 400 mg/d dose and 50 percent for the 800 mg/d dose (p = 0.026). The study initially described by Demetri et al. in 2002 had a subsequent report by Heinrich et al. in 2003 that reported median follow up of 594 days.[46, 47] The OS reported for all patients was 85 percent at 76 weeks, with a median EFS of 17 months.[47]

Two phase III efficacy studies of imatinib are currently ongoing. Both of these are published in abstract form only. Both compare different dosing regimens of imatinib. Blay and colleagues are testing continuous vs. intermittent imatinib dosing schedules[52] and Rankin et al. are testing 400 mg/d vs. 800 mg/d.[53] Results are preliminary. The study of 400 mg/d vs. 800 mg/d involved 746 participants and reports 2-year OS at 78 percent (CI 73-82%) for the 400 mg/d group and 73 percent (CI 68-77%) for the 800 mg/d group. The 2-year PFS is 50 percent (CI 45-55 percent) for the 400 mg/d group and 53 percent (CI 47-58 percent) for the 800 mg/d group.

The only significant difference in outcomes identified between different dosing schedules was that seen in the Verweij et al. (2004) study where patients on 800 mg/d have significantly higher PFS rates.[49] Two studies have evaluated the potential to increase the dose from 400 mg/d to 800

mg/d in the setting of tumor progression at the lower dose. In a subsequent abstract report of the Verweij et al. (2004) study, 220 of 473 patients on the lower dose of 400 mg/d progressed; 65 percent (143) crossed over to the 800 mg/d dose with 26 percent progression-free at one year.[50] Toxicity required dose reductions in 31 percent of those who crossed over to the higher dose. In the ongoing Rankin et al. phase III trial, 164 patients on the lower dose of 400 mg/d progressed; 54 percent (88) crossed over to the 800 mg/d dose with median PFS of 4 months and median OS of 19 months after crossover. The overall interpretation of these studies is that crossover is feasible with some tumor responses.

Imatinib Plus Surgery

Four studies were identified that reviewed the role of imatinib in peri-surgical settings (Table 5) including neoadjuvant imatinib prior to planned tumor resection, adjuvant imatinib for tumors at high risk of recurrence after complete resection, and palliative imatinib after incomplete surgery. Only one of these was prospective (Bumming [55]), while the others were retrospective reviews of prospectively collected registry data. The summary finding from these small lower-quality studies is that neoadjuvant and adjuvant imatinib is feasible. The efficacy is still to be determined.

Table 4. Summary of efficacy of imatinib for GIST

Study ID	Imatinib dose [length of follow up]	No. of patients, age [66]), sex	GIST tumor characteristics	Outcomes sought	N	%CR	%PR	%SD	%PD	%NE	Survival/ Other
Phase II											
van Oosterom et al., 2001[6] with followup in: van Oosterom et al., 2002[45]	400-1000 mg dose escalation Phase I; 800 mg Phase II [9-13 mo]	40 pts 53 [29-69] 63% M	36 had CD117-positive GIST and 4 had non-GIST STS per 2001 report; 35 had CD 117 GIST and 5 had non-GIST STS per 2002 report Liver metastases 75% 60% previous chemotherapy; 10% previous XRT	Tumor response- RECIST CT/PET Toxicity- NCI CTC v2.0	GIST 36 Non-GIST STS 4		53%	47% 25%	11% 75%		At minimum followup of 9-13 mo, 81% of GIST patients were still on imatinib
Demetri, 2002[46] with repeated report in: Dagher 2002[43] and follow up in: Heinrich, 2003[47]	Randomized between 400 and 600 mg [minimum 9 mo with median 288 dys; Heinrich et al. report with 19 mo followup with median 594d]	147 pts 54 [18-83] 57% M	All tumors CD117 positive 100% unresectable or metastatic 90% with recurrence at the time of imatinib therapy Prior therapies: 98% Surgery 51% Chemotherapy 15% Radiotherapy	Mortality: K-M Tumor response: MRI/CT RECIST QOL/PM: (ECOG) Adverse events: CTC 2.0	All 400 mg dose (73) 600 mg dose (74)	0% 0% 0%	54% 49% 58%	28% 32% 24%	14% 16% 11%	5% 3% 1%	OS at 76 wks = 85% median EFS = 17 mo
Verweij, 2003[48]	800 mg [median followup =13+ mo for GIST pts and 2 mo for	51 (27 GIST 24 STS) 53 [21-75] 67% M	GIST = CD 117 positive All advanced, unresectable or metastatic	Tumor response: RECIST Time to progression	GIST 27 Non-GIST STS 24	4% 0%	67% 0%	19% 29%	11% NR		GIST with 73% DFS at 1 yr

Study ID	Imatinib dose [length of follow up]	No. of patients, age [66]), sex	GIST tumor characteristics	Outcomes sought	N	%CR	%PR	%SD	%PD	%NE	Survival/ Other
	non-GIST STS pts]		Prior therapies: 88% surgery 24% radiotherapy 71% chemotherapy								
Verweij, 2004[49] with followup in: Zalcberg, 2004[50] (abstract)	Randomized between Imatinib 400 mg/d vs. Imatinib 800 mg/d (given as 400 mg twice daily) [median followup 760d]	946 473 @400 mg/d 59 [49-67] 60% M 473@800 mg/d 60 [49-68] 61% M	GIST = CD 117 positive All advanced, unresectable or metastatic 400 mg qd: 87% surgery 6% radiotherapy 33% chemotherapy 800 mg qd: 83% surgery 8% radiotherapy 33% chemotherapy	Progression free survival-KM Overall survival-KM Tumor response-CT or MRI RECIST Toxicity-NCI CTC version 2.0	400 mg/d (473) 800 mg/d (473)	5% 6%	45% 48%	32% 32%	13% 9%	5% 5%	1 yr survival: 400 mg/d = 85% 800 mg/d = 85% 2 yr survival: 400 mg/d = 69% 800 mg/d = 74% 2 yr PFS: 400 mg/d = 44% 800 mg/d = 50% (p = 0.026) 220 of the 473 patients on 400 mg/d have PD and 143 have crossed to 800 mg/d; 26% progression free at 1 year with med TTP 78d compared to 203d prior to crossover; toxicity required dose reduction in 31%; interpretation is that crossover is feasible
Casali, 2004[51] (abstract)	Unk dose [9 mo]	135 65 [unk] 70% M (129 patients evaluable)	GIST = CD 117 positive All advanced, unresectable or metastatic	Tumor response-RECIST	129		44% (PR + CR)				PFS > 70%

Study ID	Imatinib dose [length of follow up]	No. of patients, age [66]), sex	GIST tumor characteristics	Outcomes sought	N	%CR	%PR	%SD	%PD	%NE	Survival/ Other
Phase III											
Blay, 2004[52] (abstract)	Unk doses One year of imatinib then randomized between continuous imatinib vs. interruption of imatinib until progression then restart [6 mo]	159 Age unk 61% M	Advanced GIST expressing a KIT or PDGFRa mutation	Progression free survival Tumor response	159 Randomized to continuous N = 23 Randomized to intermittent N = 23	10%	42%	36% 0% 21%	6%	6%	Reintroduction of imatinib yielded tumor control in all 5 who progressed
Rankin, 2004[53] and Patel 2003[54] (abstracts)	Randomized between Imatinib 400 mg/d vs Imatinib 800 mg/d (given as 400 mg twice daily) [median 768d, range 70-1029d]	746 Age unk Gender unk	Metastatic GIST	Progression free survival Overall survival-KM Tumor response	400 mg						2 yr survival: 400 mg/d = 78% (CI 73-82%) 800 mg/d = 73% (CI 68-77%) 2 yr PFS: 400 mg/d = 50% (CI 45-55%) 800 mg/d = 53% (CI 47-58%) 164 patients at 400 mg/d have progressed and 88 /164 crossed over to 800 mg/d, with 7% PR and 29% SD after crossover; after crossover, median PPS = 4 mo and median OS = 19 mo

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable; RECIST and CR/PR/SD/PD – see Table 2; NCI = National Cancer Institute; CTC = Common Toxicity Criteria; K-M = Kaplan-Meier; QOL = Quality of life; PM = performance measure; ECOG = Eastern Oncology Cooperative Group performance status scale; OS = overall survival; EFS = event-free survival, see Table 2; STS = soft-tissue sarcoma; NR = not reported; DFS = Disease free survival, see Table 2; Unk = unknown; PFS = progression-free survival, see Table 2; CI = 95% confidence interval

Table 5. Summary of efficacy of imatinib plus surgery for GIST

Study ID	Imatinib dose [length of follow up	No. of patients, age [66], sex	Gist tumor characteristics	Outcomes sought	N	%CR	%PR	%SD	%PD	%NE	Other
Phase II											
Bumming, 2003[55]	400 mg/d [mean = 10.7 mo]	17 57 [10-74] 88% M	All patients were high risk or overtly malignant GIST (metastatic disease at presentation) # of prior surgeries 0 = 1 pt 1-3 = 14 pts > 4 = 2 pts non-surgical therapy not stated	Tu response: CT RECIST or PET	Neoadjuvant 1		100% (1 pt)				
					adjuvant 5	100% (5pts)					
					palliative 11		73% (8 pts)	9% (1 pt)	18% (2 pts)		
Retrospective reviews											
Rutkowski, 2003[56]	400-800 mg/d [median followup 7 mos for patients receiving imatinib and 23 mo overall]	35 55 [36-79] 69%M	Patients with C-KIT+ GIST that had liver metastases as documented in the database; all patients underwent surgery 57% complete resection 17% microscopically incomplete resection 26% open biopsy only	Tu response: CT RECIST	Surgery 3						
					imatinib 32		50%	37.5%	12.5%		

Study ID	Imatinib dose [length of follow up	No. of patients, age [66], sex	Gist tumor characteristics	Outcomes sought	N	%CR	%PR	%SD	%PD	%NE	Other
Scaife, 2003[57]	76% 400 mg imatinib 6% 600 mg Imatinib 18% 800 mg imatinib [median follow up from imatinib treatment to resection = 10mo; median follow up after surgery = 6mos]	17 56 [35-76] 59% M	unresectable intraabdominal c-KIT+ GISTS by CD117 immunohistochemistry. patients who received imatinib pre-operatively (neo-adjuvantly) and then underwent surgical exploration for tumor resection	Tu response: Radiographic change on CT (criteria unclear), PET, or peri-operative pathological specimens; Feasibility of surgical resection after treatment with imatinib	CT: 17 PET: 17 pathology: 17	6% 55% 12% 94% (complete resection)	70% 27% 65%	18% 2% 18%	6% 0% 6%		
Wu, 2003[58]	400-800 mg/d [median followup 18 mo with range 4-81]	57 61 [42-83] 51%M	Diagnosed with GIST and receiving a related surgical resection	OS: Kaplan-Meier Tu response: criteria unclear	all patients who underwent surgery, regardless of use of imatinib patients who underwent surgery and were exposed to imatinib in the adjuvant (for high risk disease; N = 3) or palliative (metastatic disease at resection or relapse; N = 26) settings	57 29	82% complete resections Not clearly stated	 85% with initial PR or SD			

Quality of Life (QOL) on Imatinib with GIST

None of the studies reviewed reported formal QOL analyses. Only Demetri et al. reported any outcomes that could be categorized as QOL.[46] This study looked at the effect of imatinib on Eastern Cooperative Oncology Group (ECOG) performance status (Table 6), comparing scores between baseline and 4 months. Some authors consider performance status to be a crude measurement of QOL.[67] At baseline 42 percent of participants were ECOG 0 and 19 percent were ECOG 2-3. This substantially improved after imatinib, such that at 4 months 64 percent of participants were ECOG 0 and 5 percent were ECOG 2-3.

Table 6. The Eastern Cooperative Oncology Group (ECOG) performance status scale

0 = fully active
1 = restricted in strenuous activity only
2 = unable to work; up and about more than 50% of waking hours
3 = confined to bed or chair more than 50% of waking hours
4 = completely disabled; totally confined to bed or chair

Adverse Effects/Harms

Adverse effects that are possibly or likely associated with imatinib for GIST are described in Table 7. The most common adverse effects are edema, nausea, and diarrhea. The edema is predominantly superficial, with some authors breaking this out to highlight the periorbital edema commonly described with imatinib. Few patients (≤ 36 percent) experienced any grade 3 or 4 toxicity at lower doses, and when they did this was predominantly hematological or hemorrhage (≤ 8 percent). These studies were often conducted in patients with bulky, advanced GIST, making it difficult to ascertain which adverse events were truly due to imatinib and which might have occurred due to the disease process itself. Toxicity was somewhat more common at the higher doses, with 800 mg/d being the most toxic dose fully described. These toxicities compare favorably to those of traditional cytotoxic agents.[28, 31, 32]

Table 7. Percentages of patients reporting adverse events on imatinib dose and grade (gd). The first three pages of this table reflect the adverse events reported in the first three studies and the next 3 pages reflect the second three studies.

	Demetri et al.						Dagher (representation of Demetri et al. 2002 data) All adverse events reported in this study were those that occurred in ≥ 10% of patients regardless of suspected relationship to treatment				Verweij et al. 2003	
Grade	Any grade %			Grade 3 or 4 %			Any grade %		Grade 3 or 4 %		any grade%	Grade 3 or 4 %
Drug	Imatinib						Imatinib				Imatinib	
Dosage	400 mg	600mg	all pts	400 mg	600 mg	all pts	400 mg	600 mg	400 mg	600 mg	400 mg	400 mg
Any adverse event with suspected relation to study drug	97	99	98	21	22	21						
Edema or fluid retention	71	77	74	1	1	1	71	76	6	3	84	0
superficial edema							71	76	4	0		
Pleural effussion or ascites							6	4	1	3		
periorbital	45	50	48	0	0	0						
Leg	26	15	20	0	0	0						
Face	8	12	10	1	0	1						
Other site	7	14	10	0	0	0						
Eyelid	7	8	8	0	0	0						
Hemorrhage	11	14	12	4	5	5	18	19	5	8	53	4
Tumor hemorrhage	1	4	3	1	4	3	1	4	1	4	43	4
Cerebral hemorrhage	0	0	0	0	0	0	1	0	1	0		
Upper GI tract	4	3	3	4	1	3	6	4	4	1	37	6
Hematologic												
Anemia	6	12	9	1	3	2						
Neutropenia/granulocytopenia	8	5	7	7	3	5						
Leukopenia	6	4	5	3	0	1						
Thrombocytopenia											55	14

	Demetri et al.						Dagher (representation of Demetri et al. 2002 data) Aall adverse events reported in this study were those that occurred in ≥ 10% of patients regardless of suspected relationship to treatment				Verweij et al. 2003	
Grade	Any grade %			Grade 3 or 4 %			Any grade %		Grade 3 or 4 %		any grade%	Grade 3 or 4 %
Drug	Imatinib						Imatinib				Imatinib	
Dosage	400 mg	600 mg	all pts	400 mg	600 mg	all pts	400 mg	600 mg	400 mg	600 mg	400 mg	400 mg
Digestive												
Diarrhea	40	50	45	1	3	2	56	60	1	4		
Flatulence	19	24	22	0	0	0	16	23	0	0		
Vomiting	14	12	13	0	1	1	22	23	1	3		
Abdominal pain	26	26	26	1	0	1	37	37	7	3		
Vomiting	14	12	13	0	1	1	22	23	1	3		
Dyspepsia	10	12	11	0	0	0						
Loose stools	7	10	8	0	0	0						
Constipation												
Taste disturbance	3	14	8	0	0	0	1	14	0	0		
Abdominal distension	6	5	5	0	0	0						
Esophageal reflux	1	7	4	0	0	0						
Nasopharyngitis							12	14	0	0		
Skin												
Pruritus	3	5	4	0	0	0						
Photosensitivity	0	5	3	0	0	0					33	6
Dermatitis or rash	25	37	31	3	3	3	26	38	3	3	80	12

	Demetri et al.						Dagher (representation of Demetri et al. 2002 data) All adverse events reported in this study were those that occurred in ≥ 10% of patients regardless of suspected relationship to treatment				Verweij et al. 2003	
Grade	Any grade %			Grade 3 or 4 %			Any grade %		Grade 3 or 4 %		any grade%	Grade 3 or 4 %
Drug	Imatinib						Imatinib				Imatinib	
Dosage	400 mg	600 mg	all pts	400 mg	600 mg	all pts	400 mg	600 mg	400 mg	600 mg	400 mg	400 mg
Whole body												
Fatigue	30	39	35	0	0	0	33	38	1	0		
Headache	19	32	26	0	0	0	25	35	0	0	41	4
Arthralgia	1	7	4	0	0	0						
Pain	6	1	3	0	0	0	11	10	1	0		
Blurred vision	6	1	3	0	0	0					20	
Pyrexia							12	5	0	0		
Insomnia								11	0	0	64	12
Chills												
Increased lacrimation	7	12	10	0	0	0	6	11	0	0		
Anorexia												
Dizziness												
Cough												
Dyspnea												
Muscle cramps							30	41	0	0		
Myalgia or musculoskeletal pain	37	42	40	0	0	0	19	11	3	0		
Infection												
Neutropenic fever												
Upper respiratory tract infection							6	11	0	0		
Neurologic												
Paresthesia	1	7	4	0	0	0						
Metabolic												
Renal or genitourinary												
Abnormal liver-function results	6	5	5	3	3	3						

	Verweij et al. 2004				van Oosterom et al. 2001 most relevant side effects (gd 2 and 3) during first 8 wks				van Oosterom et al. 2002 Update on 2001 paper with data at 8 months	
Grade	gd1-gd2 %	gd3-gd4 %	gd1-gd2 %	gd3-gd4 %	% of patients who experience relevant side effect				gd1-gd2 %	gd3-gd4 %
Drug	Imatinib		Imatinib		Imatinib				Imatinib	
Dosage	400 mg		800 mg		400 mg N=8	600 mg N=8	800 mg N=16	1000 mg N=8	Across dose ranges (400-1000 mg)	
Any adverse event with suspected relation to study drug	67	36	49	51						
Edema or fluid retention	23	14	78	9	0	25	31	38		10
Superficial edema										
Pleural effussion or ascites										3
Periorbital									40 (not graded)	
Leg										38
Face										
Other site										
Eyelid										
Hemorrhage	8	0	15	8						
Tumor hemorrhage										
Cerebral hemorrhage										
Upper GI tract										
Hematologic										
Anemia	55 27	10 1	81	17						12
Neutropenia/granulocytopenia	20 13	0.04 3	36	7						17
Leukopenia	27 13	0.03 0	45	2						10
Thrombocytopenia	4 0	0 0	5	0					3	

	Verweij et a.l 2004				van Oosterom et al. 2001 Most relevant side effects (gd 2 and 3) during first 8 wks				van Oosterom et al. 2002 Update on 2001 paper with data at 8 months	
Grade	gd1-gd2 %	gd3-gd4 %	gd1-gd2 %	gd3-gd4 %	% of patients who experience relevant side effect				gd1-gd2 %	gd3-gd4 %
Drug	Imatinib		Imatinib		Imatinib				Imatinib	
Dosage	400 mg		800 mg		400 mg N=8	600 mg N=8	800 mg N=16	1000 mg N=8	Across dose ranges (400-1000 mg)	
Digestive										
Diarrhea	46	1	17	1					15	
Flatulence										
Vvomiting	23	0	36	3	25	0	6	25		25
Abdominal pain										
Vomiting	23	0	36	3	25	0	6	25		25
Dyspepsia										
Loose stools										
Constipation	11 4	0.01 0	17	1						
Taste disturbance										
Abdominal distension				2						
Esophageal reflux										
Nasopharyngitis										
Skin										
Pruritus	12 4	0 0	15 8	1 0						
Photosensitivity										
Dermatitis or rash	24	0	42	6	0	13	25	25		30

	Verweij et al. 2004				van Oosterom et al. 2001 Most relevant side effects (gd 2 and 3) during first 8 wks				van Oosterom et al. 2002 Update on 2001 paper with data at 8 months	
Grade	gd1-gd2 %		gd3-gd4 %		gd1-gd2 %		gd3-gd4 %		% of patients who experience relevant side effect				gd1-gd2 %	gd3-gd4 %
Drug	Imatinib				Imatinib				Imatinib				Imatinib	
Dosage	400 mg				800 mg				400 mg N=8	600 mg N=8	800 mg N=16	1000 mg N=8	Across dose ranges (400-1000 mg)	
Whole body														
Fatigue	62		1		69		12							30
Headache	16		0		13		1							
Arthralgia	11	2	0	0	15		1							
Pain														
Blurred vision														
Pyrexia	8	3	0.01	0	13	3	1	0						
Insomnia														
Chills														
Increased lacrimation														
Anorexia	16	8	0.02	0	25	13	8	0					15	
Dizziness	9	1	0	0	11	2	0.004	0						
Cough	11	2	0	0	11	3	1	0						
Dyspnea	0	8	0.03	0	0	13	3	1	0	0	0	13		
Muscle cramps														
Myalgia or musculoskeletal pain	25		0		26		0							
Infection														
Infection	7	7	0.03	0	9	8	4	0						
Neutropenic fever									0	0	6	0		
Upper respiratory tract infection														
Neurologic														
Paresthesia														
Metabolic														
Renal or genitourinary	9	3	0	0	48	5	2	0.6						
Abnormal liver-function results														

Predictors of Response

All reports on predictors of response or survival from the clinical studies of imatinib for GIST are shown in Tables 8-10. Response predictors were divided into three groups: (1) tumor characteristics, (2) radiological studies predicting GIST response to imatinib, and (3) other clinical prognostic factors. Three factors had data from two studies evaluating each factor (c-kit and PDGFRA mutational status, positive emission tomography (PET) as a complementary tool to computed tomography (CT), and performance status). All other factors evaluated were presented in one study only.

The most relevant predictors of response relate to the mechanism of action of imatinib (Table 8). Patients with GIST (presumably expressing CD117) were more likely to respond to imatinib than patients with other soft tissue sarcomas (presumably CD117 negative).[48] Patients with identified c-kit mutations were less likely to progress on imatinib and had longer overall survival.[59] Both exon 11 and exon 9 mutations positively influenced response to imatinib.[47, 59] Some other genetic predictors such as SPRY4 and MAFbx may be clinically relevant, but current studies are too small to make valid conclusions at this time.[60]

Early response on PET scan at day 8 predicted clinical response to imatinib (Table 9).[61] Patients with positive evidence of response on day 8 PET had a 92 percent PFS rate, while those with no evidence of response had a 12 percent PFS rate. Studies of the differential performance of PET vs. CT were mixed, one suggesting PET was a more sensitive indicator of the presence of tumor and the other suggesting no difference between the two modalities. In the high quality study comparing multiple types of PET and CT, combined PET-CT was the most sensitive.[62, 63] This study was specifically evaluating the differential ability of the modalities to predict response to imatinib.[62] Promising new radiological techniques are on the horizon, some of which may be more sensitive than CT (e.g., angio-echography with BR-1 contrast) and some of which may be as good as CT but less invasive (e.g., ultrasound with perfusion software).[64, 65]

Other clinical factors associated with poor response to imatinib included poor performance status, lower doses of imatinib, renal dysfunction, and prior chemotherapy (Table 10).[47, 49]

Table 8. Tumor characteristics predictive of disease response or survival

Characteristic	Prognostic factor	Studies indicating an association and quality	Strength of association with tumor response	Strength of association with survival
c-kit mutation	c-kit mutation present vs. absent	Debiec-Rychter et al., 2004 (quality = 6/6)[59]	TTP: patients with C kit mutations less likely to progress (p = 0.03)	patients with c-kit mutations with longer OS (p = 0.015)
	Exon 11 mutation	Debiec-Rychter et al., 2004 (quality = 6/6)[59] Heinrich et al., 2003 (quality = 6/6)[47]	EFS: c-kit exon 11 mutation with median EFS 849d; all other mutations EFS 327d HR 0.17 (0.10-0.29) p < 0.0001*	 HR 0.04 (0.01-0.12) p < 0.0001*
	Exon 9 mutation	Heinrich et al., 2003 (quality = 6/6)[47]		HR 0.31 (0.11-0.89) p = 0.0289*
Other genes	Gene SPRY4 (found to be downregulated by imatinib in in vitro pre-clinical studies)	Frolov et al., 2003 (quality = 1/6)[60]	SPRY4 was "dramatically" decreased in 4/5 patients with PR, expressed at high levels in the 2/2 non-responders, and initially decreased then returned to high levels in the 1/5 PR patient who had an early relapse	
	Gene MAFbx (found to be upregulated by imatinib in in vitro pre-clinical studies)	Frolov et al., 2003 (quality = 1/6)[60]	Variable responses (2/5 PR patients had included levels of MAFbx; initially increased and then returned to pre-treatment levels in the patient with PR but early relapse; not changed at all in the one PD patient)	
Pathology	GIST vs. other STS	Verweij et al., 2003 (quality = 6/6)[48]	GIST with 73% DFS at 1yr Median TTP STS = 58d	

Abbreviations: TTP = time to progression; OS = overall survival; EFS = event free survival; HR = hazard ratio; STS = soft tissue sarcomas; DFS = disease-free survival

*In this study hazard rations greater than one are predictive of poorer prognosis

Table 9. Radiological predictors of disease response or survival

Characteristic	Factor	Studies indicating an association and quality	Strength of association with tumor response	Strength of association with survival
PET	Evidence of response on Day 8 PET	Stroobants et al., 2003 (quality = 4/6)[61]	1 year PFS: Positive evidence of response on PET at 8 days PFS = 92%, No response to PET at 8 days PFS = 12%, p = 0.00107	
PET vs CT (RECIST)	Differential ability to predict response to imatinib (by month of assessment)	Antoch et al., 2004 (quality = 5/5)[62]	PET 1 mo 85% 3 mo 100% 6 mo 100% CT 1mo 44% 3 mo 60% 6 mo 57% Combined PET/CT 1mo 95% 3 mo 100% 6 mo 100% Side-by-side PET and CT 1mo 90% 3 mo 100% 6 mo 100%	
	Performance of F-FDG PET and CT in staging GISTS	Gayed et al., 2004 (quality = 1/5)[63]	Sensitivity: CT 93% PET 86% p = 0.27 Positive predictive value: CT 100% PET 98% p = 0.25	
Angio-echography with BR-1 contrast vs. CT (RECIST)	Ability to predict clinical outcome and therapeutic effect of imatinib	De Giorgi et al., 2004 (abstract)[64]	Documented tumor response: CT = 46% Angio-echography = 82%	
Ultrasound with perfusion software and contrast injection vs. CT	Ability to predict clinical outcome and therapeutic effect of imatinib	Lassau et al., 2004 (abstract)[65]	No significant difference between CT and ultrasound's ability to document response	

Abbreviations: PET = FDG positive emission tomography; CT = computed tomography; TTP = time to progression; OS = overall survival; EFS = event free survival; HR = hazard ratio; RECIST = RECIST response criteria – see Table 2; NS = not significant

Table 10. Other clinical predictors of disease response or survival

Characteristic	Prognostic Factor	Studies indicating an association and quality	Strength of association with tumor response	Strength of association with survival
Performance status	Poor vs. good performance status at baseline	Heinrich et al., 2003 (quality = 6/6)[47] Verweij et al., 2004 (quality = 6/6)[49]	HR: 1.57 (1.18-2.1) p = 0.0022* No significant relationship	HR: 2.8 (1.57-5.02) p = 0.0005*
Dose of imatinib	600 mg vs. 400 mg dose	Heinrich et al., 2003 (quality = 6/6)[47]	HR: 0.57 (0.36-0.91) p = 0.018*	
Creatinine	Elevated creatinine at baseline vs. not elevated	Heinrich et al., 2003 (quality = 6/6)[47]		HR: 2.9 (0.86-9.80) p = 0.0866*
Prior chemotherapy	Prior chemotherapy vs. no prior chemotherapy	Heinrich et al., 2003 (quality = 6/6)[47]		HR: 2.6 (0.98-7.06) p = 0.0558*

Abbreviations: PET = FDG positive emission tomography; CT = computed tomography; TTP = time to progression; OS = overall survival; EFS = event free survival; HR = hazard ratio; RECIST = RECIST response criteria – see Table 2; NS = not significant

*In this study hazard rations greater than one are predictive of poorer prognosis

Discussion

In this section we summarize the findings of the review in terms of answering the key questions initially posed, and then discuss the clinical and research implications of these data.

Prior to the advent of imatinib, unresectable or metastatic GIST had an exceptionally poor prognosis.[5, 16] Single-agent doxorubicin, single-agent ifosfamide or combination chemotherapy including these agents were the standard of care since GIST was treated in the same manner as any other sarcoma of soft tissues, although response rates were exceedingly low and short-lived, and generally indicative of the ineffectiveness of any conventional chemotherapy approach.[31, 32] Importantly, these chemotherapeutic studies were done in an era when it was hard to differentiate GIST from other soft tissue sarcomas (STS), so the reported response rates are for the entire group of tumors rather than GIST specifically.[16] With the discovery of CD117 and the KIT or PDGFRA tyrosine kinase proteins on the surface of most GISTs, it became possible to designate any individual STS as GIST or as some other histopathologic subtype of STS. The use of imatinib for CD 117 positive advanced GISTs quickly followed. Efficacy and tolerability have only been compared with historical norms from studies of the more general advanced STS therapy of single-agent doxorubicin, single-agent ifosfamide, or combination chemotherapy. Head-to-head comparisons are not available. Given the great improvements in efficacy witnessed in the phase II and III studies, it is unlikely that head-to-head studies would be conducted or would be ethical. More recent analyses are starting to evaluate the role of imatinib in the adjuvant and neo-adjuvant settings, but this work is early and the role of imatinib in these peri-surgical settings remains unclear.

1. *In patients with GIST, what is the effect of imatinib compared to doxorubicin and ifosfamide on overall survival, disease free survival, time to progression, CR, PR, and quality of life?*

There is consistent convincing evidence from high quality phase II and III studies that imatinib for unresectable or metastatic GIST yields complete response (CR) rates of 0-6 percent, partial response (PR) rates of 45-67 percent, and stable disease (SD) rates of 19-47 percent, with an overall response rate (CR + PR) of 49-71 percent. This is substantially better than historical response rates of 15-34 percent (median 26 percent) for single agent doxorubicin and 7-38 percent (median 26 percent) for single agent ifosfamide (studies of general STS).[31] Experts argue that these comparative efficacy rates are high, noting that the GIST-subgoup within the studies of all STS had response rates in the 0-5 percent range.[68, 5] Exact estimates are difficult to determine due to the historical difficulty with distinguishing GIST from other STS prior to the advent of CD117.

Data from the Verweij et al. (2004) study[49] provides the most complete estimates of survival. One-year overall survival (OS) with imatinib can be estimated at 85 percent and 2-year OS at 72 percent; 2-year progression-free survival (PPS) with imatinib can be estimated at 44-50 percent depending upon the imatinib dose. The most widely reported survival estimates from earlier STS studies are from a phase III trial of combination chemotherapy with doxorubicin, dacarbazine, ifosfamide, and mesna (MAID) vs. doxorubicin and decarbazine for advanced STS.[37] In that study, 1-year OS is approximately 45-50 percent for both groups (estimated from

Kaplan-Meier graphs) and 2-year OS is approximately 25-30 percent %; 2-year PFS was approximately < 5 percent. In the NICE systematic review of non-imatinib treatments for advanced GIST, OS was 72 percent (18-100 percent) at 1 year, 40 percent (30-66 percent) at 2 years, and 16 percent (0-40 percent) at 3 years.[16] The interventions reviewed were heterogeneous including novel chemotherapeutics and/or standard sarcoma chemotherapy regimens; studies included patients with GISTs and a broad range of other histopathologic subtypes of STS. In the Bramwell et al. meta-analysis of randomized trials of doxorubicin-containing regimens for advanced STS overall, median survival ranged from 7.3-12.7 months and OS was not reported.[32]

The conventional tumor response criteria of CR and PR represent the conventional goal in oncology to eliminate the tumor to the greatest extent possible in an effort to ultimately improve patient outcomes and survival. Recently there is an evolving change to this convention. Current studies suggest that if targeted therapy stabilizes disease, it may prolong survival despite failure of the tumor to shrink sufficiently to show a response according to conventional criteria.[69] In essence the tumor is changed into a more chronic disease, quiescent until resistance occurs.

The role of imatinib in other clinical settings is still unclear. Clearly, complete surgical resection is still the therapy of choice in patients with primary presentation of limited GIST in whom the disease can be completed resected without unacceptable functional morbidity.[3, 16] It is unknown whether pre-operative (so-called "neo-adjuvant") imatinib can make complete resection more feasible and recent studies are just starting to address this question (Table 5). The role of adjuvant imatinib for resected GISTs at high risk of recurrence is also unknown, but is being addressed by a large, prospective, placebo-controlled clinical trial sponsored by the US NCI that is ongoing (ACOSOG trial Z9001). Meta-analysis of adjuvant doxorubicin-containing regimens for general STS suggest that they improve recurrence rates but not overall survival;[28] subsequent studies of adjuvant ifosfamide-containing regimens suggest the same.[29]

Quality of life outcomes have been poorly studied. The only reported relevant findings were from one study;[46] patients receiving imatinib had demonstrable improvement in performance status with only 42 percent of patients fully functional at baseline and 64 percent fully functional 4 months after initiation of imatinib.

2. *In patients with GIST, what is the effect of imatinib compared to doxorubicin (Adriamycin) and ifosfamide on adverse effects, tolerability, and compliance with treatment?*

Imatinib has far fewer adverse effects (any grade and grade 3/4) compared with single-agent doxorubicin or ifosfamide. Imatinib's most common side effects are edema, nausea and diarrhea, which are rarely grade 3 or 4. Any grade 3 or 4 side effects occur in ≤36 percent of patients at the 600 mg daily dose or lower and hemorrhagic or hematologic effects occur in ≤8 percent. At 800 mg daily, 30-50 percent of patients will have grade 3 or 4 toxicities, which are primarily hemorrhagic or hematologic effects. Compliance with treatment was not reported.

Doxorubicin's most concerning toxicities are its cardiotoxicity, nausea/vomiting, mucositis, and myelosuppression. In the Bramwell et al. meta-analysis of randomized trials of doxorubicin-containing regimens for advanced GIST, toxicities were variably reported and included severe

hematologic 28-53 percent and moderate/severe nausea/vomiting 2-42 percent.[32] At total doxorubicin doses < 400 mg/m^2 the incidence of congestive heart failure (CHF) is 0.14 percent.[70] The incidence of CHF increases as the cumulative dose increases; at total doses of 550 mg/m^2 the incidence is 7 percent and at 700 mg/m^2 the incidence is 18 percent. Ifosfamide's most frequently reported toxicities include bladder toxicity, nephrotoxicity, nausea/vomiting myelosuppression, and neurotoxicity. Summary toxicity data were not identified in the literature; grade 3-4 toxicity from individual studies varied widely with increasing rates as doses increased. For example, Antman et al. reported neurotoxicity in 19 percent of patients who received 2g/m^2 x 4 days,[34] and van Oosterom et al. reported up to 63 percent with grade 3/4 leukopenia at 3g/m^2 x 4 days.[35] In the MAID combination, the incidence of severe life-threatening toxicities includes the following: leucopenia (89 percent), granulocytopenia (79 percent), thrombocytopenia (26 percent), anemia (22 percent), nausea/vomiting (19 percent), mucositis (9 percent), neurotoxicity (6 percent), and diarrhea (4 percent).[37] Life-threatening cardiotoxicity due to doxorubicin was not seen in the MAID phase III trial. Further, these chemotherapeutic agents also have the inconvenience and increased cost of requiring parenteral (intravenous) administration directly under the supervision of an oncologist and treating nurse.

3. *What patient or tumor characteristics distinguish treatment responders from non-responders and have potential to be used to target therapy?*

There was little consistency in studies seeking to identify possible prognostic factors. No factor was evaluated in more than two studies. The most relevant predictors of response relate to the mechanism of action of imatinib. Patients with GIST (presumably expressing CD117) are more likely to respond to imatinib than patients with other STS.[48] Patients with identified c-kit mutations, especially those on exons 11 and 9, are less likely to progress on imatinib and have longer overall survival.[47, 59] These findings are striking, since c-kit mutations including those on exons 11 and 9 lead to the more malignant GIST phenotype when imatinib is not used.[12 17-21]

Radiological predictors suggestive of response may be useful for prognostication and tailoring therapy. In particular, early response on PET scan at day 8 predicts clinical response to imatinib.[61] In the highest quality study of two similar studies, PET was more sensitive than CT at determining tumor response and combined PET-CT was most sensitive.[62] A second study of lower quality contradicted the finding of PET vs. CT. Other clinical predictors were varied, unrelated to the mechanism of action of imatinib, and uncorroborated.

Taken together, these data suggest that the patients most likely to get benefit from imatinib are those with c-kit mutations, especially those on exons 11 or 9. Early response PET may be a good indicator of overall treatment effect.

Current State of Clinical Use

Imatinib is quickly becoming the standard of care for unresectable and/or metastatic GIST worldwide. A recent National Comprehensive Cancer Network (NCCN) 2004 Task Force Report and Guideline advocated its use[3], as does the NICE systematic review.[16] The NCI clinical guide at www.cancer.gov does not recommend imatinib or other specific therapy for recurrent/metastatic GIST currently; [30] experts argue that this guideline is out of date and does

not represent current clinical care. According to the NCCN, baseline CT with or without PET is advocated, with three monthly reassessments to evaluate response to therapy. Imatinib is started at a minimum dose of 400 mg daily; dose escalation can be considered for tumor progression or disease recurrence. The NCCN recommends imatinib as the only chemotherapy for primary, metastatic, postsurgical adjuvant, or progressive recurrent treatment. The use of imatinib in the post-operative adjuvant setting remains the focus of ongoing clinical research studies.

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The optimal dose continues to be unclear. The current FDA indication is for 400–600 mg daily.[43] The randomized phase II trial of 400 mg vs. 600 mg daily does not show clear benefit of one dose over another.[43, 46] In the randomized phase III trial of 400 mg vs. 800 mg, there was a trend (in the U.S./Canadian trial) or a statistically significant increase (in the European/Australasian trial) in progression-free survival but not overall survival with the higher imatinib dose. However, the higher dose had significantly more adverse effects.[71,72,73,54] Patients on the lower dose were able to cross over to the higher dose when disease progressed and some anti-tumor activity was seen in these crossover patients.[49, 50]

Current phase III studies are investigating the question of 400 mg vs. 800 mg daily further and the option for intermittent dosing. Early analyses of the two dosing levels suggest that the two doses have equal efficacy, and that increasing to the higher dose in the setting of tumor progression at the lower dose is possible.[53, 54] In the trial of continuous vs. intermittent dosing, patients are provided continuous imatinib for the first year (dose unknown) and then randomized to continue the imatinib or stop the imatinib and resume it in the setting of tumor progression.[52] It is too early to interpret the results from this study. Based on current information, the current dosing plan of 400 mg daily on an uninterrupted schedule and then increasing to 800 mg daily in the setting of progressive tumor appears to be a rational strategy.

Additional clinical trials are underway to determine whether adjuvant imatinib for one, two or three years post-resection will impact progression-free survival.[74]

Forthcoming Evidence and Implications for Future Research

Understanding of the role of imatinib in GIST is quickly evolving. At the American Society of Clinical Oncology (ASCO) meeting in June 2005, 19 abstracts included information specifically about imatinib for the treatment of GIST. Published ASCO abstracts were reviewed to develop a horizon view of emerging data and upcoming clinical trials. Of the 19 abstracts, 3 were case reports,[75-77] 3 were retrospective reviews[78-80], and 2 focused on radiographic issues[81, 82] and therefore excluded from this discussion. Eleven abstracts were fully reviewed.

Three abstracts present information from the S0033 Phase III trial of 400 mg vs. 800 mg of imatinib for the management of advanced GIST.[83-85] A total of 746 participants were randomized in this study. On the 400mg arm (N=350), 62 percent had at least one dose delay and 10 percent had at least one dose reduction unusually due to side effects such as rash, edema, or gastrointestinal hemorrhage.[83] On the 800 mg arm, 56 percent had at least one dose delay and 44 percent had at least one dose reduction due to edema, nausea, and fatigue. Crossover from 400 mg to 800 mg was allowed for non-responders at the lower dose. This occurred in 112 patients with 23 percent having at least one dose delay and 16 percent one dose reduction (data

available on 77 of 112 crossover patients). Pathological data and tumor response information were available for 414 participants.[84] Patients with KIT positive GIST (N=377) and KIT negative GIST (N=14) had similar response rates and PFS at 2 years (KIT+ 49 percent, KIT- 43 percent). Patients with non-GIST histology (N=16) had substantially poorer outcomes with 13 percent PFS at 2 years. Median survival for GIST patients had not been reached at the time of the abstract analysis; median survival for non-GIST patients was 8 months. Unblinded results of this RCT are pending. Among KIT+ GIST patients, 86 percent had *KIT* mutations and 1 percent had PDGFRA mutations, with an overall mutation frequency of 87 percent.[85] Patients with the exon 11 mutant KIT isoform were more likely to have an objective response (OR) to imatinib (OR=67 percent) than those with the exon 9 mutation (OR=40 percent) or no mutation (OR=39 percent, p=0.0022). There was also a trend toward better overall survival for patients with the exon 11 mutation. Current analyses of S0033 suggest that there are differential rates of toxicity for 400 mg vs. 800 mg, that crossover to higher dose imatinib is feasible when patients progress on the 400 mg dose, that imatinib is efficacious for both KIT+ and KIT- GIST but not tumors other than GIST, and that patients with *KIT* exon 11 mutations have the best prognosis.

The BFR14 study is a phase III trial of the French Sarcoma Group evaluating continuous vs. interrupted imatinib for the management of advanced GIST; two abstracts regarding this trial were presented.[86, 87] Patients who were progression-free after one year were randomized to either discontinue imatinib until evidence of further progression or to continue imatinib until evidence of progression. Thus far, 198 patients have been enrolled in the study and 58 patients were free from progression at one year and therefore randomized. This study is ongoing and final results are pending, however at the time of the ASCO abstract, 66 percent of patients in the interrupted treatment plan arm had progressed vs. 15 percent of patients who received uninterrupted imatinib (median follow up 21 months, $p<0.0004$ for difference in PFS).[87] Imatinib reintroduction allowed tumor control in 79 percent of patients. One year OS rates were similar (89 percent vs 87 percent, p=0.46). Evaluation for predictors of OS and PFS among enrolled participants demonstrated that elevated lymphocyte count (HR 1.25, 95 percent CI 1.04-1.49), CD34 negative phenotype (HR 5.18, 95 percent CI 1.98-13.6), and performance status $\geq$1 (HR 5.32, 95 percent CI 1.75-16.2) independently predicted OS while liver metastases ((HR 0.40, 95 percent CI 0.20-0.83) and CD34 positive phenotype (HR 0.45, 95 percent CI 0.22-0.93) independently predicted higher PFS.[86] Current analyses of BFR14 suggest that PFS is poorer when imatinib is interrupted, but that reintroduction of the drug allows further tumor control in the majority of patients, thus far without a difference in overall survival.

ACASOG Z9000 is a phase II evaluation of adjuvant imatinib at 400 mg for 1 year in patients with primary high risk GIST following complete resection.[88] Data on 106 evaluable patients who had been in the study for at least one year were presented in one ASCO abstract (median age 58, 67 percent male). Toxicity profiles were similar to other studies of imatinib; nineteen (18 percent) patients did not complete therapy either due to toxicity (N=6) or withdrawal of consent (N=12). This study is ongoing with survival outcomes pending. The current assessment of Z9000 is that adjuvant imatinib is well tolerated.

A phase II efficacy study including 7 patients with unresectable advanced GIST treated with imatinib 400 mg daily at Oncology Hospital "Siglo XXI" IMSS (Mexico) demonstrated an

overall response rate of 72 percent.[89] One patient achieved a complete response. Average follow up was 9 months (range 5–10).

In addition to the predictors of response and survival described in the S0033 and BFR14 trials, there were three other abstracts addressing predictors of response. In an analysis of 15 advanced GIST patients treated with imatinib at 400 mg daily, PDGFR overexpression (N=10 of 15) predicted shorter time to progression (p=0.02).[90] In an analysis of 68 cases of advanced GIST, p53 mutations were identified in 12 cases (18 percent). Two-year OS was better in p53 mutation negative patients than p53 positive patients (89 percent vs. 75 percent, p=0.0156).[91] In an analysis of 55 resected GIST patients, survival was predicted by size of the tumor mass (tumor <5cm with 3-year OS 86 percent and >5cm 66 percent, p=0.023) and mitotic activity (<10 mitoses per high power field 3-year OS=90 percent, >10 OS=64 percent, p=0.0368).[92] In this study, patients with a deletion or insertion of KIT exon 11 had poorer 3-year OS of 35 percent vs. 64 percent for all other patients (p=0.0383). These findings contradict those of the S0033 study where exon 11 mutations predicted better survival.[85] Overall, molecular predictors analyses presented at ASCO suggest that KIT status does not affect GIST response, that the effect of KIT exon 11 mutations on outcomes with imatinib is unclear, that we have a lot to learn about the CD34 phenotype, and that p53 may portend poorer prognosis in GIST.

Only one abstract focused on side effects of imatinib for GIST. Mean corpuscular volume (MCV) was monitored for 33 advanced GIST patients treated with 400 mg daily.[93] A total of 42 percent developed an elevated MCV over the upper limit of normal, without coincident anemia or explanation. This side effect was asymptomatic.

Overall, preliminary review of this forthcoming evidence suggests that new data will soon be available to inform ideal dosing, ideal dosing schedules, timing with surgery, and likelihood of response. In addition to ongoing phase II and III studies, future clinical studies will likely focus on refining the molecular predictors of response and developing related tests for routine clinical use. The other active area of GIST clinical research is to develop radiological tests that are less invasive and are more predictive of response to imatinib and outcome. Given the growing number of recent articles about neoadjuvant and adjuvant imatinib, further prospective and coordinated studies of the use of imatinib in this clinical context need to be undertaken. Further, many patients with GIST still have progressive or recurrent disease despite imatinib. Imatinib resistance is a main topic in CML research. Research on imatinib resistance in GIST is likely to be forthcoming, including an understanding of the molecular basis of this resistance and new methods to overcome it. And, like in CML, combinations of imatinib and other chemotherapies will likely be studied in the future.

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Excluded Articles

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Appendix A:
MEDLINE Search Strategy

Database: Ovid MEDLINE(R) <1966 to September Week 3 2004>
Search Strategy:
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1 (gefitinib or erlotinib or iressa or tarceva or lapatinib or ekb-569 or ci-1033 or zd1839 or osi-774).mp. (817)
2 exp lung neoplasms/ or carcinoma, non-small-cell lung/ (96461)
3 1 and 2 (339)
4 randomized controlled trial.pt. (194192)
5 controlled clinical trial.pt. (67292)
6 Randomized Controlled Trials/ (34359)
7 Random Allocation/ (51911)
8 Double-Blind Method/ (79820)
9 Single-Blind Method/ (8433)
10 or/4-9 (329367)
11 Animal/ not Human/ (2838957)
12 10 not 11 (311915)
13 clinical trial.pt. (392148)
14 exp Clinical Trials/ (159166)
15 (clinic$ adj25 trial$).tw. (103424)
16 ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw. (76365)
17 Placebos/ (23320)
18 placebo$.tw. (86217)
19 random$.tw. (294378)
20 Research Design/ (38965)
21 (latin adj square).tw. (2126)
22 or/13-21 (693867)
23 22 not 11 (643785)
24 23 not 12 (342333)
25 Comparative Study/ (1152523)
26 exp Evaluation Studies/ (499768)
27 Follow-Up Studies/ (288858)
28 Prospective Studies/ (178265)
29 (control$ or prospectiv$ or volunteer$).tw. (1483791)
30 Cross-Over Studies/ (15073)
31 or/25-30 (2964552)
32 31 not 11 (2271429)
33 32 not (12 or 24) (1817997)
34 12 or 24 or 33 (2472245)
35 3 and 34 (241)
36 limit 35 to english language (216)
37 from 36 keep 1-216 (216)
38 (imatinib or gleevec or glivec or STI571).mp. (1613)
39 exp leukemia, myeloid, chronic/ (9737)

40 38 and 39 (718)
41 40 and 34 (286)
42 limit 41 to english language (250)
43 from 42 keep 1-250 (250)
44 (gist or (gastro$ adj2 stromal adj (tumo$ or cancer$))).mp. (1111)
45 38 and 44 (236)
46 45 and 34 (98)
47 limit 46 to english language (88)
48 from 47 keep 1-88 (88)

Appendix B:
Quality Criteria

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups random?
   - Adequate approaches to sequence generation
   - Computer-generated random numbers
   - Random numbers tables
   - Inadequate approaches to sequence generation
   - Use of alternation, case record numbers, birth dates or weekdays
2. Was the treatment allocation concealed?
   - Adequate approaches to concealment of randomization
   - Centralized or pharmacy-controlled randomization
   - Serially-numbered identical containers
   - On-site computer based system with a randomization sequence that is not readable until allocation
   - Other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients
   - Inadequate approaches to concealment of randomization
   - Use of alternation, case record numbers, birth dates or weekdays
   - Open random numbers lists
   - Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
3. Were the groups similar at baseline in terms of important prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors blinded to the treatment allocation?
6. Was the care provider blinded?
7. Was the patient blinded?
8. Were the point estimates and measure of variability presented for the primary outcome measure?
9. Did the analyses include an intention to treat analysis?

Quality criteria for assessment of observational studies

From the York CRD handbook (http://www.york.ac.uk/inst/crd/crd4_ph5.pdf)

Cohort studies

Is there a sufficient description of the groups and the distribution of prognostic factor?
Are the groups assembled at a similar point in their disease progression?
Is the intervention/treatment reliably ascertained?
Were the groups comparable on all-important confounding factors?
Was there adequate adjustment for the effects of these confounding variables?
Was a dose-response relationship between intervention and outcome demonstrated?
Was outcome assessment blind to exposure status?
Was follow-up long enough for the outcomes to occur?
What proportion of the cohort was followed-up?
Were dropout rates and reasons for dropout similar across intervention and unexposed groups?

Case-control studies

Is the case definition explicit?
Had the disease state of the cases been reliably assessed and validated?
Were the controls randomly selected from the source of population of the cases?
How comparable are the cases and controls with respect to potential confounding factors?
Were interventions and other exposures assessed in the same way for cases and controls?
How was the response rate defined?
Were the non-response rates and reasons for non-response the same in both groups?
Is it possible that over-matching has occurred in that cases and controls were matched on factors related to exposure?
Was an appropriate statistical analysis used (matched or unmatched)?

Case series

Is the study based on a representative sample selected from a relevant population?
Are the criteria for inclusion explicit?
Did all individuals enter the survey at a similar point in their disease progression?
Was follow-up long enough for important events to occur?
Were outcomes assessed using objective criteria or was blinding used?
If comparisons of sub-series are being made, was there a sufficient description of the series and the distribution of prognostic factors?