Battling gastrointestinal stromal tumor

LIFE RAFT GROUP

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The role of patient-driven research in the GIST community

By Norman Scherzer
Life Raft Group Executive Director

The normal duties of daily life in the Life Raft Group office are repeatedly punctuated by the ringing of the telephone. An international patient is in crisis. A woman on Medicare needs further coverage explanations. A man doesn't understand his CT scan results. Patient after patient question their treatment, their options and their care.

As a patient support and advocacy organization, it is the responsibility of the LRG to assist our members in every way possible. This includes investigating areas of patient treatment that are not being examined by traditional clinical trials. One such area is the analysis of the relationship between the actual dosage of imatinib and patient survival; this is the focus of the LRG's study, "The effect of imatinib dose upon the survival of metastatic GIST patients".

To accomplish this, we created the Life Raft Group GIST Patient Registry, a patient-driven research effort based upon detailed medical updates provided by patients. The data is entered by trained staff into a comprehensive and sophisticated database.

Utilizing this registry, the Life Raft Group was first to report that imatinib had an initial success rate of 85 percent and that side-effect severity is gender related and eases over time. Finally, we were the first to report a relationship between imatinib dosage and progression free survival.

This patient registry has grown to over 900 GIST patient records, including the largest pediatric GIST data base in the world, thanks not only to the staff and volunteers who are trained to enter, analyze and interpret the data, but also to the dedication of the GIST patients who contribute. Through in-depth membership applications and medical updates sent on

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The effect of imatinib dose upon the survival of metastatic GIST patients

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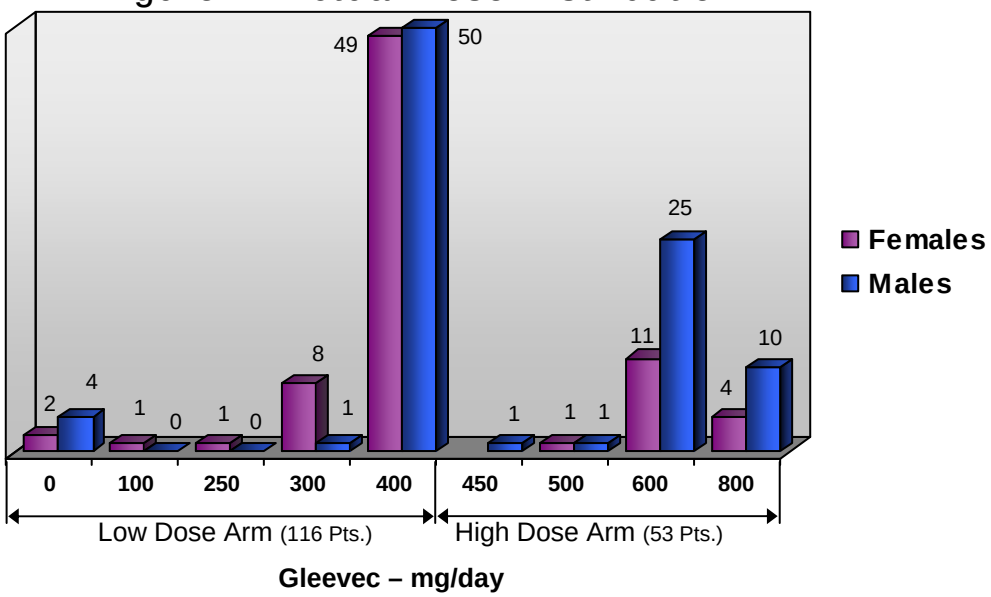
Abstract: Imatinib is a selective tyrosine kinase inhibitor that is successfully used in the treatment of gastrointestinal stromal tumors. Previous studies of low and high dose levels using starting dose analysis have shown a small statistical benefit in progression free survival (PFS) but no benefit in overall survival (OS). We investigated whether actual dose analysis produced an increased survival benefit for patients showing a clear response to imatinib therapy. A statistically significant benefit was found for PFS and OS. In addition, higher mortality rates were found for those patients that progressed early on in the study. These results suggest that increasing imatinib doses to at least 600 mg prior to progression leads to improved patient survival.

Introduction

Imatinib (STI-571, Gleevec®, Glivec®) is the front-line therapy for metastatic

Figure 1: Actual Dose Distribution



gastrointestinal stromal tumors (GIST). This selective tyrosine kinase inhibitor is orally administered on a continuous basis. Current treatment protocols call for imatinib therapy to be initiated at 400 mg daily and escalated when progression occurs[1].

"Intent-to-treat" analysis, termed starting dose analysis in this publication, is the standard method that has been used for evaluating the effectiveness of imatinib at different doses. In this type of analysis, a patient is initially prescribed a specific dose, their starting dose. All research analysis is done using this starting dose as the patient's dose regardless of any dose changes that subsequently may occur. There are several benefits to this type of analysis. If a patient cannot tolerate a high dose due to severe side-effects, it is likely that the beneficial effects of the drug are being outweighed by the unwanted side-effects. If the benefits of both dose levels are nearly similar, but the unwanted side-effects of the higher dose are too severe to tolerate, then the higher dose level is not useful. This is then reflected in the results of the trial.

Shortly after the Life Raft Group (LRG) began building our GIST patient registry we became increasingly aware of variations in the dose actually taken by patients. Most of these changes could be attributed to new physician prescriptions but some were made on the part of the patients. When this happened, some patients did not report these changes to their prescribing physician.

Table 1

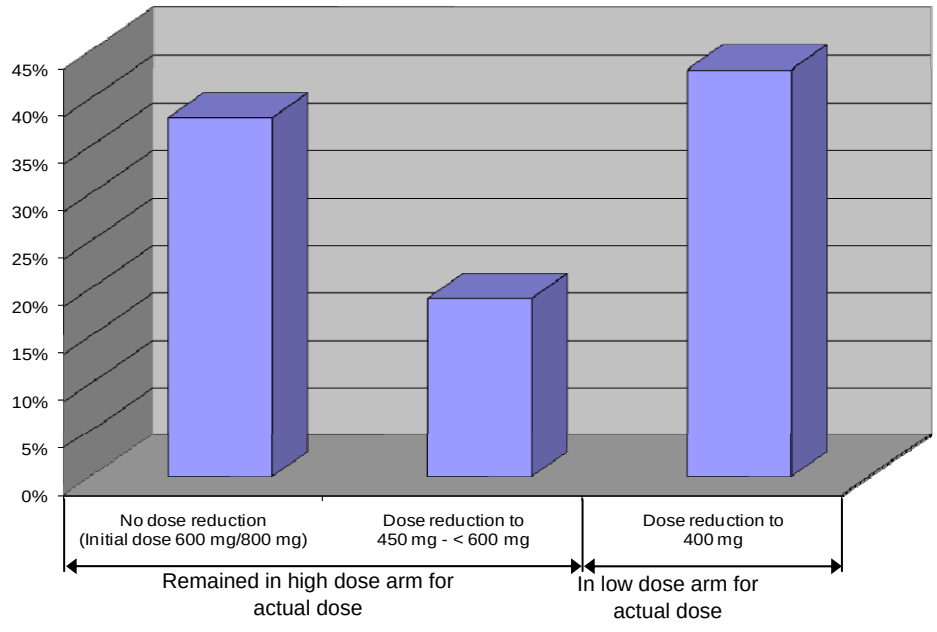
Dose reductions in the high dose group

Dose reduced to	Percent of total group
400 mg	43%
450 mg to <600 mg	19%
600 mg or 800 mg (no reduction)	38%

The reports of dose changes did not initially seem significant. LRG data and that of the formal clinical trials showed that initial response to imatinib did not appear to be dose related with about 85 percent of all patients showing some treatment benefit ranging from stability to shrinkage[2]. At this early stage, no one was aware that a subset of patients, those with exon 9 mutations, initially responds better to a higher dose of imatinib.

Due to the high percentage of patients that required dose reductions, the LRG decided to examine the difference between starting dose and actual dose. We observed that patients at a higher actual dose of imatinib, as opposed to a higher

Figure 2: Starting dose reductions for the high dose arm



The Life Raft Group

Who are we, what do we do?

The Life Raft Group is an international, Internet-based, non-profit organization offering support through education and research to patients with a rare cancer called GIST (gastrointestinal stromal tumor). The Association of Cancer Online Resources provides the group with several listservs that permit members to communicate via secure e-mail. Many members are being successfully treated with an oral cancer drug Gleevec (Glivec outside the U.S.A.). This molecularly targeted therapy represents a new category of drugs known as signal transduction inhibitors and has been described by the scientific community as the medical model for the treatment of cancer. Several new drugs are now in clinical trials.

How to join

GIST patients and their caregivers may apply for membership free of charge at the Life Raft Group's Web site, www.liferaftgroup.org or by contacting our office directly.

Privacy

Privacy is of paramount concern, and we try to err on the side of privacy. We do not send information that might be considered private to anyone outside the group, including medical professionals. However, this newsletter serves as an outreach and is widely distributed. Hence, all articles are edited to maintain the anonymity of members unless they have granted publication of more information.

How to help

Donations to The Life Raft Group, incorporated in New Jersey, U.S.A., as a 501(c)(3) nonprofit organization, are tax deductible in the United States.

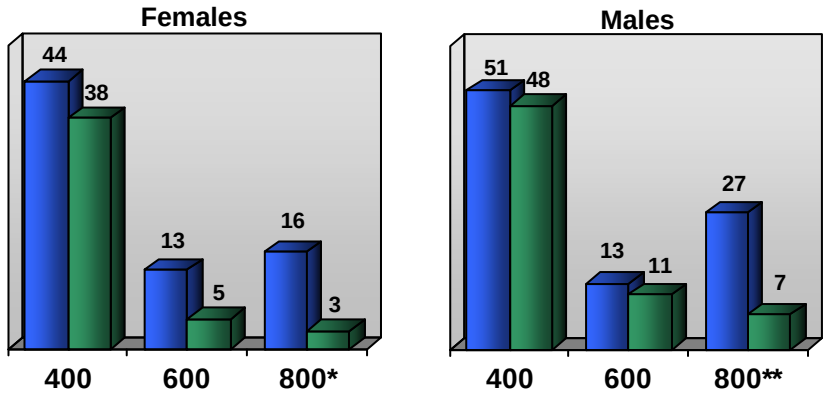
Donations, payable to The Life Raft Group, should be mailed to:

The Life Raft Group
40 Galesi Dr., Suite 19
Wayne, NJ 07470

Disclaimer

We are patients and caregivers, not doctors. Information shared is not a substitute for discussion with your doctor. As for the newsletter, every effort to achieve accuracy is made but we are human and errors occur. Please advise the newsletter editor of any errors.

Figure 3: Dose Reductions



Started **Remaining**

* 4 moved to 600 mg
9 moved to less than 600 mg
3 remained at 800 mg.

** 6 moved to 600 mg
14 moved to less than 600 mg
7 remained at 800 mg.

starting dose, seemed to experience less drug resistance. Since the side-effects of imatinib improve significantly over time[3], we questioned whether evaluating imatinib effectiveness exclusively using the starting dose is sufficient in this situation.

In November 2004, we presented our findings at the Oncology session of the Connective Tissue Oncology Society (CTOS). We observed that amongst 169 metastatic GIST patients who had demonstrated initial tumor shrinkage to imatinib and remained progression free for at least one year, that those on higher doses of imatinib continued to remain progression free at higher rates than those on lower doses. At that time, we did not evaluate OS, as opposed to PFS. Though this dataset ended in October 2004, the LRG continued to follow these patients. In November of 2007 we returned to this study group.

The objectives of the LRG's current study are to determine whether there is a correlation between imatinib dose and survival, both progression free and overall, and to evaluate the difference between using starting dose and actual dose. Concerned about the small number of patients that were able to tolerate 800 mg of imatinib, we attempted to evaluate the effectiveness of 600 mg as well as the difference between the 600 mg and 800 mg doses in a secondary analysis. In addition, we performed the same analysis of dose broken down by gender. Finally, the LRG compared the subsequent mortality rates of those patients that had relapsed at the time of the CTOS presentation in 2004 to those who had not relapsed at that time.

Methodology

Study Criteria:

The study group consists of 169 metastatic GIST patients, 77 females and 92 males, who had demonstrated initial tumor shrinkage in response to imatinib therapy and remained progression free for at least one year. The selection of the one year mark was somewhat arbitrary. In addition, to reduce ambiguity and subjectivity in determination of initial response to imatinib, those patients that presented with initial stability but no shrinkage were also excluded. These criteria were selected in an attempt to identify those GIST patients that were most likely to benefit from imatinib therapy. Data was provided by LRG members for patients that met the study criteria. Most of these 169 patients had begun imatinib from mid 2000 to 2002.

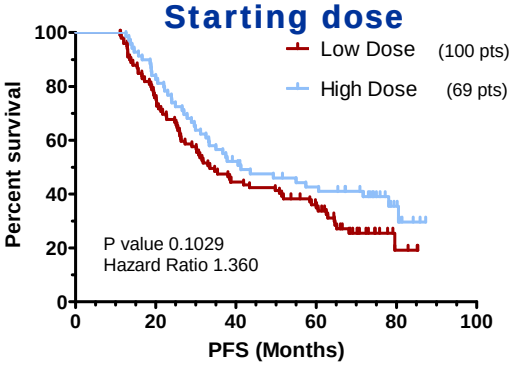
The results of this study are based upon patient reporting which could reflect some subjectivity in assessment of initial shrinkage and time of progression. There is no subjectivity in the assessment of mortality.

Evaluating Dose:

This study looked at response and survival using both starting dose (the dose that patients were prescribed when imatinib therapy was initiated) and actual dose (the dose that patients were on at the time of relapse or at their last update, if they had not relapsed). In the primary analysis, we divided patients into two dose groups; low dose and high dose. We considered all patients taking 400 mg or below as low dose and all patients taking over 400 mg as high dose. The use of the categories high dose and low dose created a larger available patient sample for inclusion (See Figure 1 (Page 1)).

Figure 4a: Progression free survival

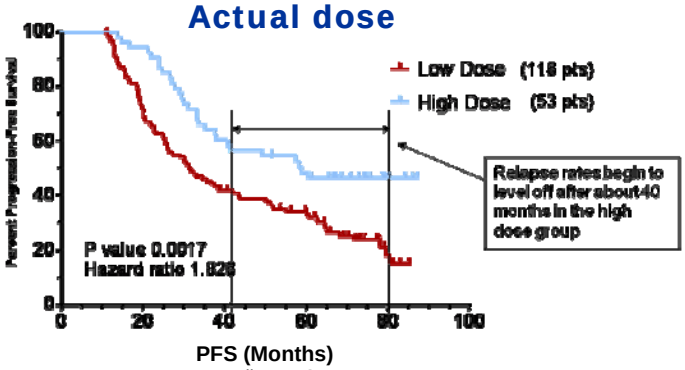
Starting dose



Median PFS
Low dose 33.5 months
High Dose 41.2 months
Difference = 7.7 months

Figure 4b: Progression free survival

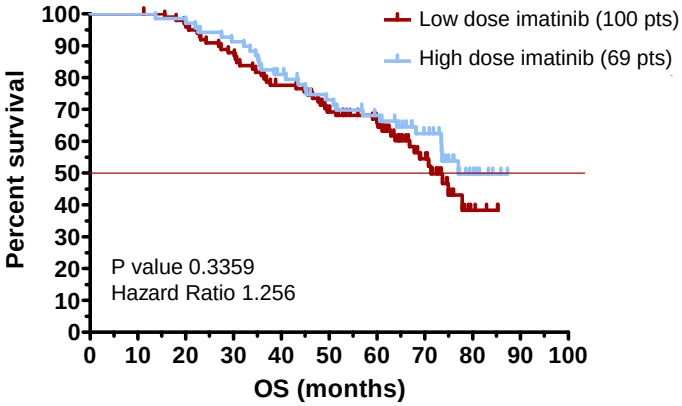
Actual dose



Median PFS
Low dose 31.5 months
High dose 58.8 months
Difference = 27.3 months

Figure 5a: Overall survival

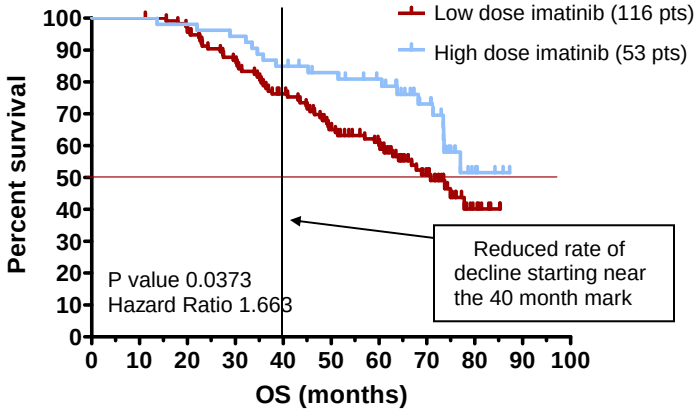
Starting Dose



Median Survival
Low dose - 71.3 months
High dose - 77 months
Difference = 5.7 months
(Not statistically significant)

Figure 5b: Overall survival

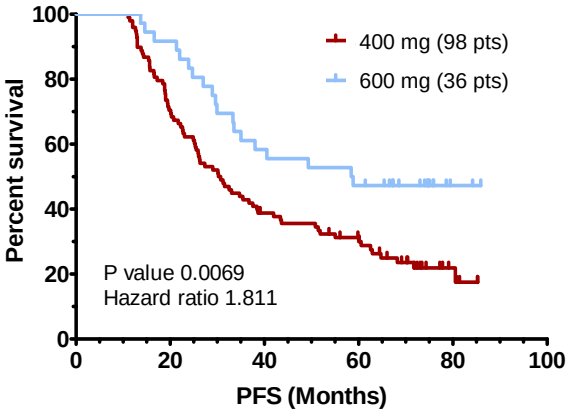
Actual Dose



Median Survival
Low dose - 70.8 months
High dose - Undefined

Figure 6a: Progression free survival

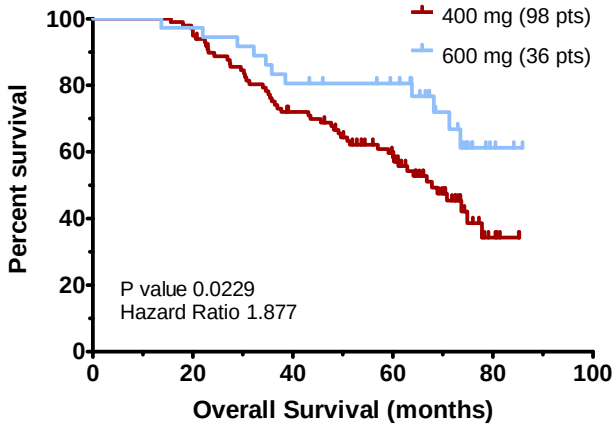
Actual Dose- 400 mg vs. 600 mg



Median PFS
Low dose - 30.2 months
High dose - 58.6 months

Figure 6b: Overall survival

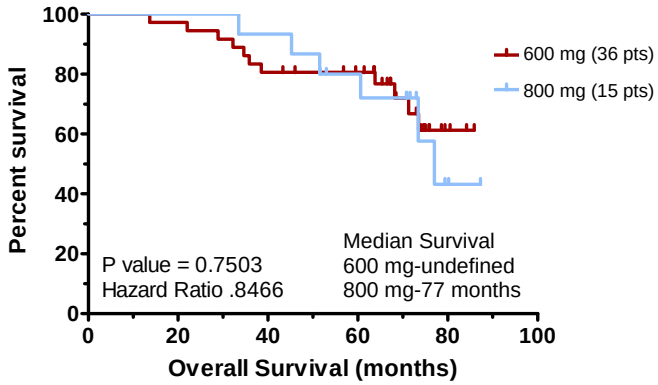
Actual Dose- 400 mg vs. 600 mg



Median Survival
400 mg - 67.8 months
600 mg - undefined

Figure 6c: Overall survival

Actual Dose– 600 mg vs. 800 mg



Acknowledgements

We are thankful to the worldwide community of clinicians and researchers who critiqued the raw data and raw bullet points that formed the basis of this article. We would particularly like to thank Dr. Martine Van Glabbeke and Dr. Peter Reichardt, for their early guidance and encouragement.

We would note that none of these scientists have yet seen the actual article and that the analysis and conclusions are the sole responsibility of the Life Raft Group.

Finally, we are indebted to the 169 patients who contributed their medical histories to form the data base for this study, particularly including the 73 whose final contribution was the report of their death.

Analysis

Dose Changes:

In the LRG study, 43 percent of the patients that were initially in the high dose arm had dose reductions that moved them into the low dose arm. Of the patients that remained in the high dose group, 19 percent of them had dose reductions, but remained in the range of the high dose arm and 38 percent had no dose reductions (See Table 1 and Figure 2(Page 2)).

Of those that initiated treatment in the low dose arm, 14 percent had dose increases that moved them into the high dose arm prior to progression. Only 9 percent of the patients that started on 400 mg required a dose reduction. Note that if a patient's imatinib dose was increased due to progression, they were counted as having progressed at the dose that they were prior progression. They were not subsequently included in the high dose arm. Actual dose distribution may be seen in Figure 1 (Page 1).

Males were better able to tolerate higher imatinib doses than females with only 19 percent of females remaining at the 800 mg dose. However, despite this relatively greater tolerance, only 28 percent of the males in this sample were able to remain on 800 mg. Eighty-five percent of the males that initiated treatment at 600 mg were able to remain at that dose level. In contrast, only 38 percent of the females that began at 600 mg were able to remain at that dose level. Dose reductions in the LRG study are shown in Figure 3 (Page 3).

Evaluation of progression free survival:

When we looked at LRG data using starting dose, we found a 7.7 month benefit for the high dose arm. This was not statistically significant with a P value of 0.1029 (See Figure 4a (Page 3)). In contrast, when we looked at LRG patients using the dose actually received, the median PFS times were 27.3 months longer in the high dose arm (58.8 months) compared to the low dose arm (31.5 months) (See Figure 4b (Page 3)).This difference was statistically significant (P = 0.0017). The hazard ratio was 1.8, indicating that patients in the low dose arm were 1.8 times as likely to have progression as those in the high dose arm.

As noted in Figure 4b (Page 3), when looking at actual dose, progression rates seem to begin leveling off in the high dose arm just after 40 months of imatinib therapy. While the slowing of progression rates seems clear, some caution should be used in interpreting this.

Evaluation of overall survival:

In the analysis of OS using starting dose, a small, but not statistically significant (P = 0.3359), benefit of 5.7 months was observed for the high dose arm (77 months) as opposed to the low dose arm (71.3 months) (See Figure 5a (Page 4)). When analyzed by actual dose, the LRG study showed a statistically significant OS benefit for the higher dose arm. The median survival was 70.8 months for the low dose arm and had not yet been reached for the high dose arm (P = 0.0373). As indicated by the hazard ratio, patients in the low dose arm had 1.66 times the risk of death compared to the high dose arm (See Figure 5b (Page 4)).

In the high dose arm of the actual dose analysis, there appears to be a reduced rate of decline in OS rates

Figure 7a: Progression free survival
Actual Dose-Females

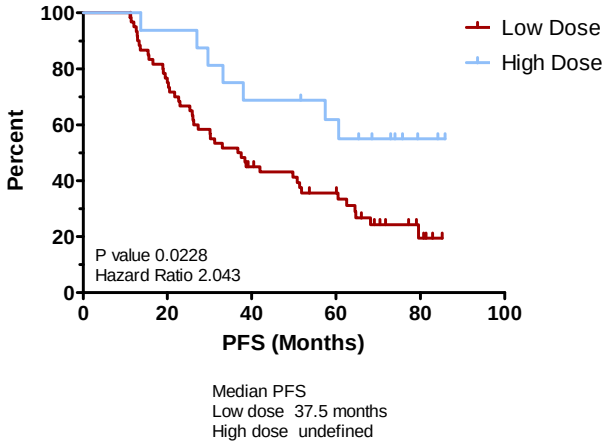


Figure 7b: Progression free survival
Actual Dose-Males

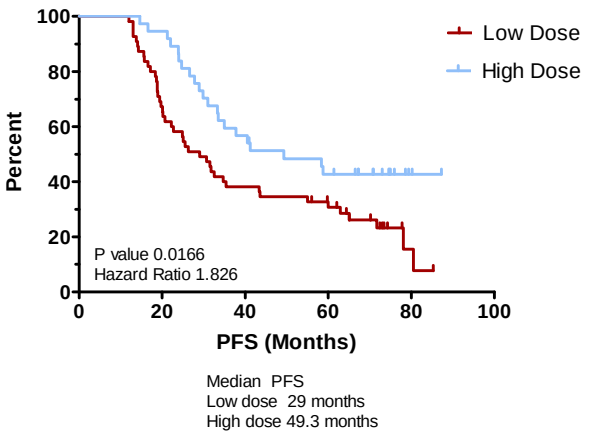


Figure 7c: Overall Survival
Actual Dose-Females

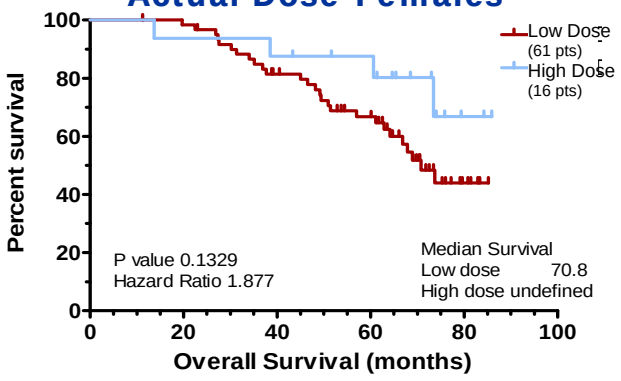


Figure 7d: Overall Survival
Actual Dose-Males

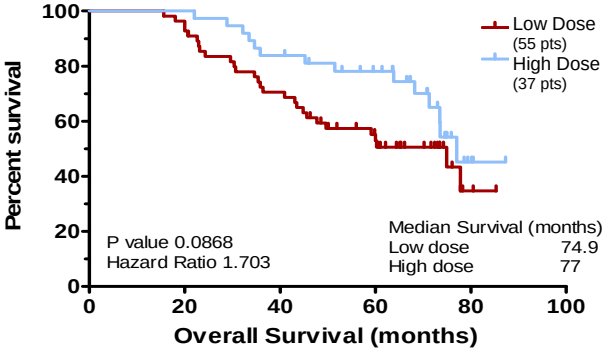
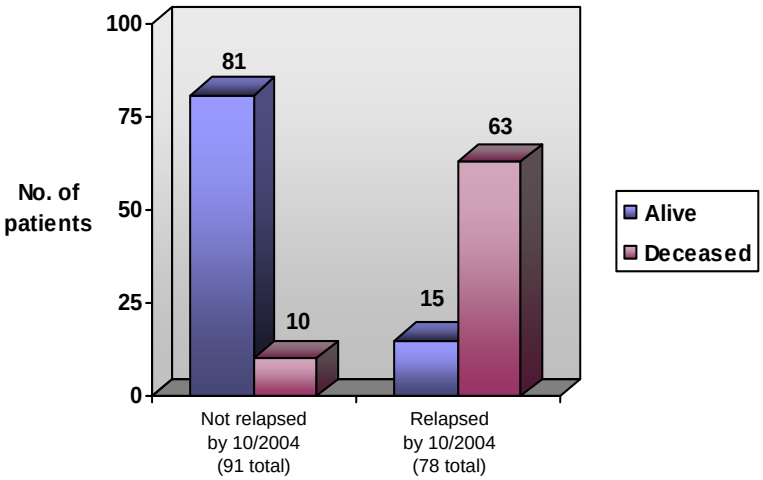


Figure 8a: Survival after relapse



occurring at approximately 40 months after the initiation of treatment (similar to the drop in progression rates) (See Figure 5b (Page 4)). This reduced rate of decline is not reflected in the low dose arm.

The effectiveness of 600 mg:

Because the 800 mg dose was not well-tolerated by women or men, we attempted to evaluate the effectiveness of 600 mg, as well as the difference in effectiveness between 600 mg and 800 mg when looking at actual dose. We compared patients taking 400 mg (98 patients) to those taking 600 mg (36 patients). In addition, we compared patients on 600 mg directly to those on 800 mg (15 patients). However, the comparison of 600 mg to 800 mg should be viewed with extreme caution due to the limited number of patients.

***Progression free survival-600 mg*:**

In this analysis of actual dose, 600 mg produced a significantly longer PFS than 400 mg (P = 0.0069). Patients taking 400 mg of imatinib had a median PFS of 30.2 months compared to 58.6 months PFS for patients taking 600 mg; a benefit of 28.4 months for the 600 mg arm (See Figure 6a (Page 4)). In addition, the median PFS for patients taking 600 mg was almost identical to the entire high dose group, 58.6 months and 58.8 months respectively. Although the numbers were too small to be definitive, there was no significant difference between patients taking 800 mg and those taking 600 mg.

Overall Survival-600 mg: Using the actual dose data, we compared the OS of patients taking 400 mg to patients taking 600 mg. Patients taking 600 mg had a statistically significant survival advantage over patients taking 400 mg (P = 0.0229). The hazard ratio was 1.877, indicating the rate of death in the 400 mg arm was 1.877 times that of the 600 mg arm (See Figure 6b (Page 4)). For comparison, the hazard ratio for OS comparing low dose to high dose was 1.663 (See Figure 5b (Page 4)). The small advantage of the 600 mg arm versus the entire high dose group (which included 800 mg patients) was not statistically significant. The median OS was 70.8 months for the low dose group and 67.8 months for patients taking 400 mg. The median OS has not been reached for either the entire high dose group or patients taking 600 mg (See Figures 5b and 6b (Page 4)).

To see if the fairly small benefit shown by the 600 mg group over the combined high dose group might be caused by the three patients in the high dose group that were taking 450 mg (one patient) and 500 mg (two patients), we removed these 3 patients from the high dose group, thus comparing patients taking 600 mg to the combined group of patients taking 600 mg and 800 mg and we found no difference when the three "mid-dose" patients were removed from the dataset (data not shown).

We also directly compared patients taking 600 mg (36 patients) to patients taking 800 mg (15 patients) and there was no significant difference between the two (P=0.75, hazard ratio .8466). The median OS of the patients taking 800 mg was 77 months and the median OS of patients taking 600 mg had not been reached (See Figure 6c (Page 4)). As noted previously, care must be taken when making this comparison due to the small sample size.

Gender:

Progression free survival-Gender: When actual dose was used to evaluate PFS, both males and females showed statistical benefit from higher doses of imatinib. The benefit was especially apparent for females.

The median PFS for males was 29 months in the low dose arm and 49.3 months in the high dose arm, a benefit for the high dose arm of 20.3 months with a hazard ratio of 1.83 (P = 0.0166) (Figure 7b (Page 5)). The median PFS for females was 37.5 months in the low dose arm and had not been reached in the high dose arm (unable to calculate the median PFS benefit at this time) with a hazard ratio of 2.04 (P = 0.0228) (See Figure 7a (Page 5)).

In a 400 mg versus 600 mg comparison, median PFS for females on an actual dose of 400 mg was 36.7 months and had not been reached in the high dose arm. (P = 0.0357) The hazard ratio was 2.187. The median PFS for males on an actual dose of 400 mg was 25.9 months and 49.3 months for males taking 600 mg. (P = 0.0505) The hazard ratio was 1.722.

Overall Survival-Gender: In contrast to the entire sample of patients, OS separated by gender did not show a statistically significant benefit for either males or females in the LRG study. Median OS for females in the low dose arm was 70.8 months and had not been reached in the high dose arm (P = 0.1329, See Figure 7c (Page 5)). The hazard ratio was

Table 2

	First Treatment Change	Subsequent Treatment Change	Total
Increased imatinib	60%	0%	60%
Sunitinib	18%	47%	65%
Nilotinib	0%	12%	12%
Surgery	9%	32%	41%
Other	13%	0%	13%

1.877. The median OS for males in the low dose category was 74.9 months and 77.0 months in the high dose category (P = 0.0868, See Figure 7d (Page 5)). The hazard ratio was 1.703.

In a 400 mg versus 600 mg comparison, median OS for females on an actual dose of 400 mg was 68.9 months and had not been reached in the high dose arm. (P = 0.0791) The hazard ratio was 2.314. The median OS for males on an actual dose of 400 mg was 60.2 months and undefined (not yet reached) for males taking 600 mg (P = 0.0961). The hazard ratio was 1.783.

Mortality rates of patients that developed resistance to imatinib:

Patients with imatinib resistance had much higher mortality rates than those that remained stable despite crossover to higher doses of imatinib and other treatments. The LRG first evaluated this group of 169 patients in October 2004. At that time, 91 remained stable on imatinib but 78 had developed progression on imatinib. Those patients that progressed moved to various other treatment regimes, often through several treatment strategies before death occurred. Sixty percent of those on a lower dose of imatinib crossed over to a higher dose, 65 percent were given sunitinib (SU11248, Sutent®), 41 percent underwent surgery and 12 percent received nilotinib (AMN107, Tasigna®) (See Table 2 (Page 6)).

Despite these subsequent treatments, the mortality rate amongst those that had progressed by October 2004 was 81 percent by December 2007 as compared to a mortality rate of 11 percent amongst those that were stable in October 2004 (See Figure 8a). Seventy-two percent of these deaths occurred within two years from the point of relapse (See Figure 8b).

Discussion

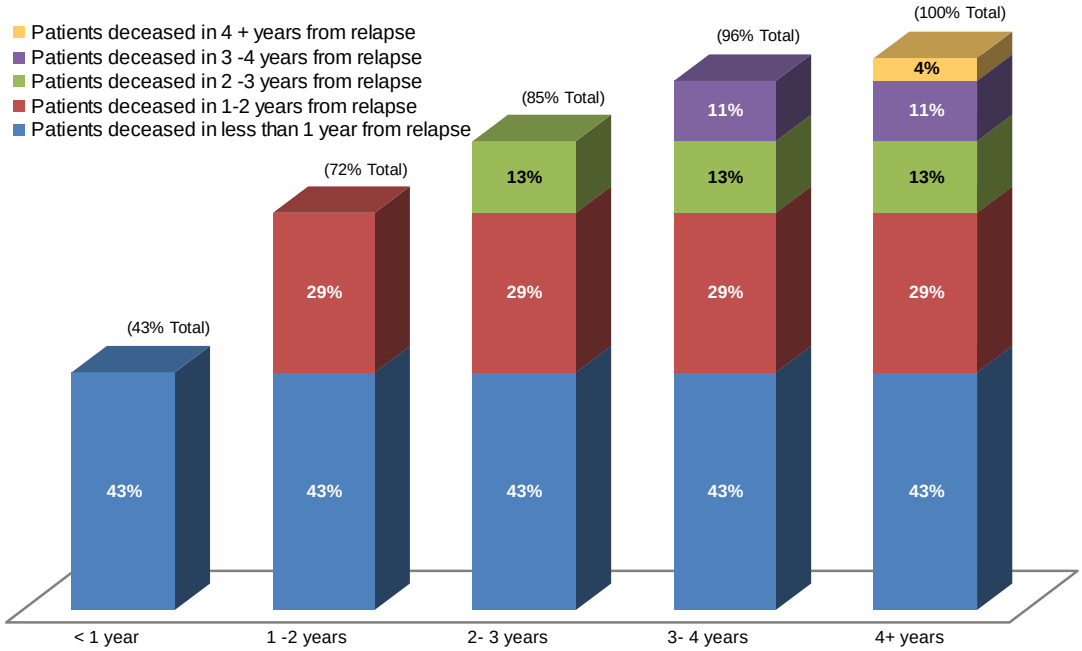
Due to the small sample size and non-random distribution of the LRG sample, care must be taken when interpreting the results. LRG patients may not be representative of the entire population of GIST patients. The use of patient-reported data and subjective progression criteria may have introduced a bias into the PFS data; however neither would affect OS data. When examining actual dose, it may be that healthier patients are better able to tolerate higher doses of imatinib and would have done better regardless of dose. More of these patients may have remained on the higher dose, thus skewing the results.

Excluding patients that progressed during the first year or that did not show initial shrinkage effectively eliminated those with primary resistance. It may be that this also eliminated a higher proportion of patients with KIT exon 9 primary mutations. This also has the effect of increasing median PFS and OS in both starting dose analysis and actual dose analysis. The result of these study criteria may be the identification of the maximum possible benefit patients might receive from high doses of imatinib therapy.

Given these limitations, there is still considerable value in the actual dose analysis of LRG Data. The LRG's analysis of actual dose as opposed to starting dose offers a unique perspective that has, to date, been overlooked in clinical trials. When collecting data on actual dose taken, patients may be more likely to report non-compliance to a patient support organization that asks in a non-threatening manner than to the doctor that controls their participation in a trial and potentially, their access to a life-saving treatment. Since the LRG is not limited by the study design of a clinical trial, we are better able to follow a patient over a long period of time and across institutional boundaries. This is especially helpful when evaluating OS.

The LRG data clearly shows an advantage to higher doses of imatinib therapy when the analysis is performed using the actual dose for both PFS and OS. These advantages are not evident when the same patient sample is analyzed using the dose at which imatinib therapy was initiated. Recognizing that the side-effects of imatinib improve over time, careful dose escalation strategies may be indicated to increase patient survival[3]. Until further analysis is performed comparing actual doses either in a clinical trial setting or by utilizing data already collected in larger studies, the LRG believes that

Figure 8b: Mortality Rates



Time from relapse to death for patients that progressed as of October 2004

the best way to improve patient survival is to initiate imatinib therapy at 400 mg and gradually increase the dose to a minimum of 600 mg as the patient is able to tolerate it.

The benefit of a higher actual dose is seen for both males and females when looking at PFS. Although OS separated by gender did not show a statistically significant benefit for either males or females in the LRG study, this may be due to the limited sample sizes. The OS hazard ratios for both males (1.703, See Figure 7d (Page 6)) and females (1.877, See Figure 7c (Page 6)) are similar to the OS hazard ratio for the combined group (1.663, See Figure 5b (Page 4)).

Although the criteria for the LRG study may have inadvertently eliminated a disproportionate number of KIT exon 9 mutation GIST patients, other studies have already indicated that exon 9 patients have greater benefit from higher doses of imatinib[15]. The current LRG study indicates that the same may be true for other GIST patients as well.

In the LRG study, fewer females than males were able to tolerate the higher doses of imatinib. Though no data was collected on the reasons for this, it suggests that females may need more careful dose escalation strategies than males. Since side-effects improve over time, the utilization of supportive medical treatments to directly control the side-effects of imatinib may prove invaluable in these strategies.

Although care must be taken in interpreting the results, there is an indication that progression rates drop over time for both progression free and OS in the high dose arm of the actual dose analysis. This is an area that needs further study to determine if it is an artifact of the LRG sample or a trend in the entire GIST population.

The analysis of LRG data indicates that 600 mg may be as effective as 800 mg of imatinib. However, due to the inability of patients to initially tolerate 800 mg of imatinib, the LRG sample size was too limited to draw any definitive conclusions. Further analysis using the actual dose in a larger dataset, such as the MetaGIST Phase III studies, is required to determine if there is a difference in effectiveness between 600 mg and 800 mg.

Current treatment protocols call for imatinib dose escalation to occur only after progression has been seen at 400 mg[16]. Although further research is required, the current LRG study indicates that it may be easier to prevent this initial resistance than it is to overcome it. A sevenfold increase in mortality was observed for those patients that developed resistance early on in this analysis (as of October 2004) despite the utilization of multiple secondary treatment regimes. This may change as new second-line treatments are developed.

In summary, LRG data indicates the best treatment strategy to maximize survival for patients with metastatic GIST consists of initiating imatinib therapy at 400 mg and slowly escalating the dose to a minimum of 600 mg prior to the onset of progression. Supportive medical treatments should be utilized to assist in the control of side-effects. Further actual dose analysis of a larger dataset would prove valuable.

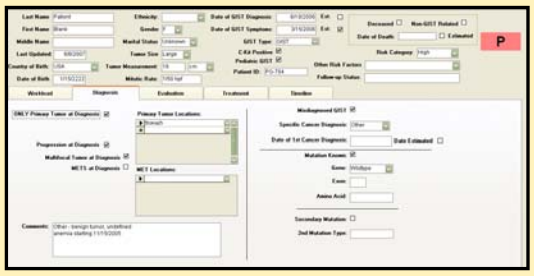
Disclaimer

The Life Raft Group has received generous grants from a number of pharmaceutical companies, including two whose drugs are cited in this study, Novartis and Pfizer. These companies had absolutely no input into the conduct or conclusions of this study which is the sole responsibility of the Life Raft Group.

PATIENTS

From Page 1

a three to six month basis, the patients tell their own story and implicitly demand an active role in their own treatment.



A sample screen of the LRG Patient Registry.

Reliability

The LRG GIST Patient Registry has developed and evolved over a period of seven years. We have learned to identify the types of information that patients and caregivers could accurately report. For example, patients/caregivers can report that their tumors have shrunk or progressed but may not always have specific measurement data. We have adopted the highest sampling standards to help ensure that those reporting are representative of the LRG as a whole. We do not utilize data unless we achieve at least a 90 percent response rate. We compare our data on common subjects to that collected by the traditional research community to ensure that the LRG is representative of the broader GIST community. We review the medical updates that patients/caregivers submit to ensure that they make sense and we follow-up with patients, often by telephone, to clarify the information. Finally, we maintain an active follow-up program to ensure that our medical records are as up to data as possible. In short we take our obligation to provide reliable and timely scientific information very seriously.

Don't forget...

Watch Jerry & Norman explain further, "The effect of imatinib dose upon the survival of metastatic GIST patients" on March 12 at 12 PM EST.

SCHERZER

CALL

Go to www.liferaftgroup.org/library_videos.html to register and submit your information. You will subsequently receive an e-mail with login information for the day of the event. Fifteen minutes before the event, log in, sit back… and enjoy!

Clinical studies: methodologies & biases

There have been three major imatinib for metastatic GIST trials. The first of these trials was the B2222 phase II trial comparing 400 mg of imatinib to 600 mg. This trial began in the summer of 2000 and enrolled 147 patients. The striking results formed the basis for the approval of imatinib in GIST in many countries. The results of this trial were reported in the *New England Journal of Medicine*, August 2002[4]. Updated results were reported in the *Journal of Clinical Oncology* on February 1, 2008[2].

The other two major trials were both phase III trials comparing 400 mg of imatinib to 800 mg. The United States/Canadian trial (S0033) started in December 2000 and enrolled 746 patients. The European/Australasian phase III trial (EORTC 62005) started a few months later and enrolled 946 patients. The results of the EORTC trial were reported in *Lancet* in September 2004[3] and the results of the US/Canadian trial were reported in the *Journal of Clinical Oncology* on February 1, 2008[5]. The two large phase III trials were designed from the onset so that the data could be combined. The combined analysis was called the "MetaGIST project" and preliminary results were reported at the 2007 American Society of Clinical Oncology (ASCO) meeting[6].

Both of the phase III trials have shown similar results. In general, they show a small benefit in progression free survival (PFS) for the high dose arm. This benefit was generally borderline for being statistically significant, sometimes showing significance and sometimes not (depending on the trial and timepoint)[3,5]. For individual differences between the two trials, interested readers should refer to the original manuscripts. For the sake of simplicity, the phase III results that we will be referring to will be the combined results as reported by the MetaGIST project.

In order to compare the LRG study and the MetaGIST study, the hazard ratios of the MetaGIST project have been adjusted (inverted) to match the reporting method used in the LRG study. For example, the inferior arm (400 mg) has 1.12 times the chance of the measured event (in this case, progression) as the superior arm. The equivalent comparison would be to say that the 800 mg group had an 11 percent risk reduction (hazard ratio of 0.89) compared to the 400 mg group.

The median PFS reported by the MetaGIST project was 19 months for the 400 mg arm (818 patients) and 23 months for the 800 mg arm (822 patients). This four month benefit for the 800 mg arm was statistically significant (P = 0.04) with a hazard ratio of 1.12.

"Once a patient is assigned to a group, they are forever counted in that group. All events, including dose changes that occur afterwards are ignored for the analysis."

The overall survival (OS) as reported by the MetaGIST project was virtually identical in the 400 mg arm and the 800 mg arm. Based on no reported difference in the OS, a small reported difference in PFS and higher toxicity in the 800 mg arm, the consensus presented in the *Journal of the National Comprehensive Cancer Network* (JNCCN) is to start patients at 400 mg and escalate to 800 mg in the event of progression[1]. The exception to this is for patients with a KIT exon 9 primary mutation; most experts feel that the MetaGIST data supports a higher dose for exon 9 patients (data not shown).

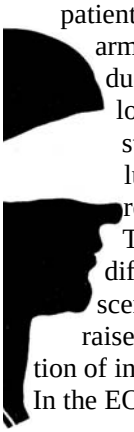
Clinical Trial Design: The gold standard in clinical trial design is a randomized trial where neither the patient nor the doctor knows which treatment the patient is receiving (a randomized double-blind trial). A step below that, but still a powerful trial design, is a randomized trial in which both the patient and the doctor know which treatment is being delivered. Randomizing patients (often done by computer), removes biases, both known and unknown.

Another aspect of clinical trials is the method used to analyze the results. The gold standard in this area has been the "intent-to-treat", or starting dose, analysis. Once a patient is assigned to a group, they are forever counted in that group. All events, including dose changes that occur afterwards are ignored for the analysis.

One of the aims of starting dose analysis is to capture "real world" results. Drugs have both beneficial effects and unwanted effects (side-effects/toxicity). It is the balance between beneficial effects and unwanted effects that determine a drug's usefulness. If a drug has nearly equal beneficial effects at a lower dose and a higher dose, but has much greater unwanted effects at the higher dose, a starting dose analysis is designed to reflect this. In this case, a starting dose analysis might show the lower dose arm to be superior to the higher dose arm.

Similar to randomization, starting dose analysis is also designed to remove biases. A classical example that is often cited is that a healthier patient might be able to tolerate a higher dose of a drug than a patient that is sicker and thus might have done better regardless of dose.

Dose Reductions: Imatinib produces clinically significant side-effects. These side-effects tend to be more pronounced in patients taking higher doses[3,5]. Trial patients assigned to the higher dose arm that require dose reductions due to side-effects are not allowed to return to the higher starting dose, even after resolution of the side-effect(s) requiring the dose reduction. This is a trial protocol and is different than the real world scenario where a doctor might raise a patient's dose after resolution of initial side-effects.



In the EORTC trial, 60 percent of the

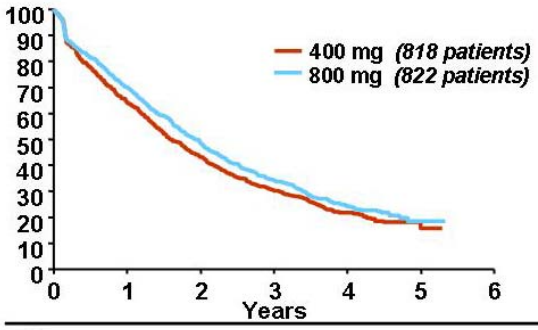
patients in the 800 mg arm had dose reductions compared to 16 percent in the 400 mg arm. In the US/Canadian trial, dose reductions in the 800 mg arm were reported as 44 percent (preliminary results) and 58 percent[5]; dose reductions in the 400 mg arm were reported in 16 percent of patients. In both trials, these were permanent dose reductions, but per starting dose analysis rules, the high dose patients with dose reductions were still counted in the 800 mg arm, even though they had dose reductions.

If the dose reductions measured in the trial represented real world results, it would suggest that the starting dose analysis might be sufficient. That is, if patients that could not tolerate a higher dose initially would never be able to tolerate a higher dose, and if 800 mg was the optimal target dose, it would help support the starting dose analysis.

There are several studies that report that imatinib-induced side-effects get better over time and that even though patients might not be able to tolerate higher doses of imatinib initially, they might be able to tolerate higher doses at a later time. The studies that report an improvement in side-effects include, but are not limited to, the EORTC phase III trial results as reported in *Lancet*[3] and an internal LRG survey (See November-December 2004 issue of the LRG newsletter). In addition, as reported in the US/Canadian data, only 16 percent of patients that had been on a lower dose of imatinib and then crossed over to 800 mg due to progression, subsequently required a dose reduction (as opposed to 60 percent given 800 mg initially).

Figure 1: PFS Data-Starting Dose

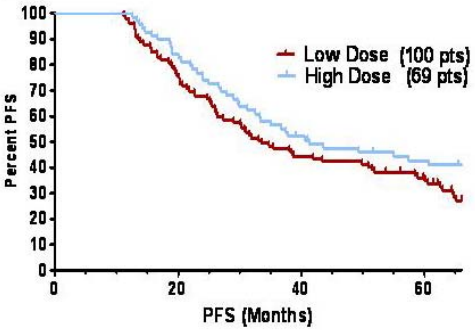
Comparison: MetaGIST Project vs. LRG



MetaGIST Project*

Median PFS (months)	19 / 23
3-year estimate (%)	30 / 34
Hazard ratio	1.12
P value (logrank test)	0.04
Median PFS benefit	4 months

*Includes pts w/primary resistance



LRG Project**

Median PFS (months)	33.5 / 41.2
3-year estimate (%)	47.5 / 56.5
Hazard ratio	1.36
P value (logrank test)	0.10
Median PFS benefit	7.7 months

**Excludes pts w/primary resistance

Comparison between LRG and MetaGIST Data

In comparing results between the LRG study and the MetaGIST study, it is very important to remember that the LRG study protocol of being on imatinib for at least 12 months (with at least some shrinkage) eliminates patients with primary resistance to imatinib. This has the effect of increasing PFS and OS times. It also causes the survival curves to have a different shape for the first year. For the MetaGIST data the curve will drop quickly (because of patients with primary resistance) while the LRG curves will be flat for the first year (because patients that progressed during the first year were not included in the LRG study).

Dose Reduction Comparison:

The LRG study divided patients into two groups; low dose (400 mg and below) and high dose (over 400 mg). Dose reductions in the LRG study appear to be similar to the phase III studies with 62 percent of LRG patients that started on high doses (600 mg or 800 mg) requiring at least one dose reduction compared to ten percent of patients that started at 400 mg.

Dose reductions in the LRG study are discussed in detail on page 3. In general, males tolerated higher doses better than females, but neither tolerated 800 mg very well. Only 28 percent of males that started on 800 mg remained on 800 mg and only 19 percent of females that started on 800 mg remained there.

In the LRG study, males seemed to tolerate a starting dose of 600 mg much better than females, with 85 percent of males able to remain at 600 mg compared to 38 percent of females.

LRG and MetaGIST data are comparable when using starting dose: We compared the 2007 LRG study with the combined results from the two large phase III GIST studies. The data from the phase III studies was combined by the MetaGIST project and includes data from 1,640 GIST patients. This meta-analysis was done using starting dose analysis. Using this type of analysis, a patient is always counted in the category that they started in regardless of the dose they actually received. As an example; if a patient starts at 800 mg, has too many side-effects and has their dose reduced to 400 mg after one month, they are still counted in the 800 mg arm, even though

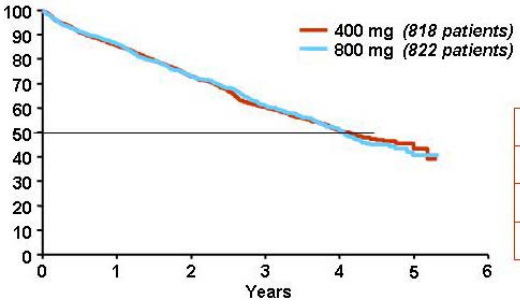
Table 1

Percentage of patients requiring dose reductions

Starting Dose Arm	US/Canadian	EORTC	LRG
400 mg / low dose arm	16%	16%	10%
800 mg / high dose arm	58%	60%	62%

Figure 2: OS Data- Starting Dose

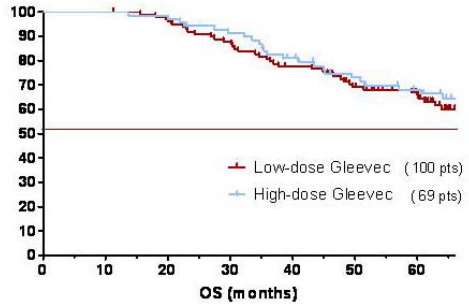
Comparison: MetaGIST Project vs. LRG



MetaGIST Project*

Median OS (months)	49 / 49
3-year estimate (%)	60 / 61
Hazard ratio	1.00
P value (logrank test)	0.97

*Includes pts w/primary resistance



LRG Project**

Median OS (months)	71.3 / 77
3-year estimate (%)	81 / 82
Hazard ratio	1.25
P value (logrank test)	0.336

**Excludes pts w/primary resistance

they received 400 mg from that time on.

The MetaGIST project compares two groups of patients; one that starts at 400 mg of imatinib and one that starts at 800 mg of imatinib. The LRG study compares a low dose group (400 mg and below) to a high dose group (over 400 mg).

We compared the PFS results from the LRG study to the MetaGIST project (See Figure 1 (Page 10)) using a starting dose analysis. Note that the beginning of the curves is different due to the LRG study's exclusion of patients with primary resistance to imatinib. Beyond that, the two curves are very similar.

Both graphs in Figure 1 (Page 10) show a modest benefit for the high dose arms, four months benefit for the MetaGIST project and 7.7 months benefit for the LRG study. The MetaGIST results were statistically significant (P = 0.04) and the LRG results (P = 0.10) were not (it is easier to demonstrate statistical significance with larger numbers like those in the MetaGIST project).

When we look at the OS comparison between the MetaGIST project and the LRG study using starting dose we see a very similar pattern (See Figure 2). The LRG curve has a straight line at the top due to the exclusion of patients with primary resistance to imatinib therapy; otherwise the two curves are very similar. Note that there is virtually no difference in either curve between the low dose arms and the high dose arms. On both graphs, the lines cross each other repeatedly.

In contrast, when the LRG data is analyzed using actual dose, a significant increase in survival is seen for the high dose arm. A reduced rate of decline in OS rates starting at approximately 40 months is seen in the LRG study that is not seen in the MetaGIST study.

PFS when analyzed using actual dose shows a 27.3 month survival benefit that is statistically significant (*P* = 0.0017). This is true for both males and females as seen on page 5. The benefit of a higher dose is also evident when analyzing OS using actual dose. The median survival for the low dose arm was 70.8 months and had not yet been reached in the high dose arm (*P* = 0.0373). The data for both PFS and OS is also presented in detail on page 5.

The MetaGIST project has several strengths that the LRG project was not able to duplicate. The trial was very large and was able to randomly assign patients to the two dose arms. They were also able to collect fairly extensive mutational data. However, starting analysis did not account adequately for permanent dose reductions in such large numbers, nor did it account for the fact that imatinib-induced side-effects improve over time. It also did not fully report on the distribution of dose reductions. The effect of this may be a dilution of data that underestimates the benefit of the higher imatinib dose.

The LRG project examined actual dose in addition to starting dose. Because the LRG is not associated with a specific trial or institution, it was possible to follow patients over a long period of time and across institutional boundaries. On the other hand, the non-randomized study design introduced the prospect of some biases. The subjective evaluation of progression and the use of patient-reported data may have affected the PFS data; however neither would affect OS data. It also may be that healthier patients were better able to remain on the higher dose and would have done better regardless of dose, thereby skewing the results of the actual dose analysis. The effect of all of these factors may be an overestimation of survival benefit for the high dose arm.

Despite the limitations of the LRG study, it is appears that there may be a significant survival benefit at the higher dose level for GIST patients. This benefit is extremely likely to extend to mutational types beyond the currently accepted benefit for exon 9 patients. Other studies have shown varied individual factors that may affect a patient's ideal imatinib dose. However, until a point is reached where a patient's optimum dose can be determined, it may be best to use careful dose escalation strategies to increase imatinib doses of all patients with metastatic GIST to a minimum of 600 mg. In the LRG study, females were less able to tolerate higher doses of imatinib. This suggests that if 600 mg is the target dose, females tend to require a more careful dose escalation strategy.

Developing individualized treatment plans

The current treatment standard for GIST patients is to start patients on 400 mg of imatinib. According to the *Journal of the National Comprehensive Cancer Network* (JNCCN) guidelines, "This dose is recommended because current data do not consistently show major differences in overall survival (OS) based on dose and because patients receiving (800 mg) have an increased risk of unacceptably severe side-effects[1]." The guidelines go on to say that "Patients could then increase to 800 mg/day of imatinib if they showed signs of progression." The JNCCN recommendations are based on the results of the GIST clinical trials, all of which used an analysis based exclusively upon starting dosage. The two major phase III clinical trials were combined into a single data set called MetaGIST.

The MetaGIST data demonstrated an advantage to higher doses of imatinib when looking at progression free survival (PFS) (a median benefit of four months). The LRG's analysis of PFS using starting dose did not show a statistically significant benefit for higher doses (median benefit of 7.7 months; P = 0.1029). However, the LRG data, when based upon an analysis using actual dosage as opposed to starting dose, showed a clear advantage to OS for the higher dose group—a finding inconsistent with that of the MetaGIST study. In addition, the LRG data showed that when using an actual dose comparison, we see a significant benefit of 600 mg compared to 400 mg but cannot determine if there is an increased benefit to 800 mg as compared to 600 mg due to the limited number of patients able to tolerate 800 mg. The MetaGIST study did not consider 600 mg of imatinib and instead compared only 400 mg to 800 mg.

The LRG data also showed that once patients using imatinib had disease progression their mortality rate was dramatically higher that that of patients using imatinib that did not have disease progression. This was despite all of the post-progression treatments, including escalation to a higher dose of imatinib and switching to sunitinib. The mortality rate for the group that had progressed as of 2004 was 81 percent compared to 11 percent for the group that had not progressed at that time.

"LRG data showed that when using an actual dose comparison, we see a significant benefit of 600 mg compared to 400 mg."

The LRG data thus strongly suggests that it is easier to prevent resistance by moving patients to a higher dosage of imatinib before resistance occurs than to try to reverse it by moving patients to a higher dosage of imatinib after it occurs.

The critical difference between the LRG and MetaGIST data is that the LRG shows a significant OS benefit and the MetaGIST shows none. This difference becomes apparent only when one analyzes the data using actual versus starting dosage. We believe that both the LRG and MetaGIST data have some bias but the practical reality is that we are unlikely to have new data from new clinical trials at any time in the near future*.

Which method introduces more bias?

• That of the LRG selection bias introduced by using a non-random group of patients which introduces the speculation that the patients that can actually tolerate a higher dose might be the healthier patients and would have done better regardless.

OR

• Counting 40 percent or more (it was 43% in the LRG study) of patients taking 400 mg or less as though they were taking a higher dose (the bias introduced by starting dose analysis).

If one leans towards accepting the MetaGIST starting dose analysis method, then there seems to be little OS benefit in a higher dose.

If one leans towards accepting the LRG use of actual dose, then it is clear that it is better to try to prevent resistance with a higher dose. This is especially true when we consider what happened to the patients in the LRG study that had progressed as of 2004 versus those that had not.

Can we optimize the dose for each patient?

A higher dose may not be right for everyone: In spite of the fact that a higher actual dosage shows a significant benefit in the LRG study, a high dose of imatinib is not right for everyone. For patients taking the same dose of imatinib, concentrations of imatinib in the blood can vary by four-fold or more [7,8]. Side-effects from imatinib also vary significantly; from very mild to life-threatening and even fatal[5]. Most side-effects are worst at higher doses including: edema, anemia, rash, fatigue, nausea, bleeding, diarrhea and others(3;5).

It is also important to note that there were some long-term responders in the low dose group including some at 300 mg. Some patients are unable to tolerate

***** *One possible design of a clinical trial would compare two randomized arms, one at 400 mg of imatinib and the other starting at 400 mg and escalating to an optimized dose. The definition of an optimized dose needs further refinement. A target dose of 600 mg might be the first step in optimizing dose. This could be complemented with drug level monitoring. Patients having unacceptable side-effects, but an acceptable drug level might be considered at their "optimal dose" at a lower dosage (such as 400 mg). Patients on 600 mg but with few side-effects and a low drug level might need 800 mg (or more) to achieve their optimal dose. Other factors such as OCT-1 activity, drug clearance and protein binding could be examined in correlative studies.*

higher doses of imatinib, even with a dose escalation strategy.

The concept of an individualized Maximum Tolerated Dose (MTD) As The Life Raft Group was preparing its dose study, we had helpful conversations with many people at various stages. As we did so, a concept started to emerge; the concept of an Individual MTD. The "maximum tolerated dose" (MTD) for imatinib was determined in phase I trials for CML and GIST. The MTD was determined to be 800 mg. But as we now know, the ability of patients to tolerate imatinib varies widely. We are aware of patients receiving doses as high as 1,200 mg and we also known that some patients could not even tolerate 100 mg. Thus, while the "official" MTD of imatinib (as determined by the trials) is 800 mg, each individual has their own MTD. It might be 300 mg, 600 mg, 800 mg or even 1,200 mg. It may be that a patient's optimum dose will have some relationship to their MTD.

"Dose escalation prior to progression to at least 600 mg of imatinib could be the most important step GIST patients take to provide extra time, perhaps as much as two years, for newer, more effective therapies to mature."

Exon 9 patients clearly benefit from a higher dose: At the present time, there is one group of patients that, with little debate, benefits from a higher dose. This group is patients with a KIT exon 9 mutation. Even when using starting dose alone as an analytical tool, the MetaGIST data shows a dramatic difference in PFS for exon 9 patients with 6 months median PFS in the 400 mg arm compared to 19 months median PFS in the 800 mg arm. The LRG study does not have sufficient mutational data to run this comparison.

Higher doses may also be more effective for patients other than exon 9: Despite the current position of the NCCN task force, there are reasons to believe that higher doses of imatinib may be more effective for many if not most GIST patients. The most compelling data comes from two recent preliminary studies (early data that has not been peer-reviewed).

The first of these is the recent study of drug levels of some phase II patients. This was presented at the 2008 ASCO Gastrointestinal meeting in January 2008 by Dr. George Demetri of Dana-Farber Cancer Institute. In this study, Dr. Demetri found that patients with blood levels in the lowest 25 percent of the group did not do as well as patients with a higher blood level. For more details about this study, see the February 2008 edition of the LRG newsletter.

The second compelling GIST study is this LRG study. While it can be argued that the data is biased by a non-randomized sample, we would submit that analyzing the dose that patients actually took offers a valuable complement to starting dose analysis. In fact, in this situation where there were so many dose reductions in the high dose arm, it may be more valuable and possibly more accurate than the starting dose analysis. Dose escalation prior to progression to at least 600 mg of imatinib could be the most important step GIST patients could take to provide extra time, perhaps as much as two years, for newer, more effective therapies to mature.

Besides these two studies there are other factors that might be used to optimize the dose for each patient. The exact relationship of these mechanisms to each other and their relationship to response need to be further studied in the context of a clinical trial. However, patients and their doctors are left with the choice between accepting the current consensus standard as is, waiting for a new trial that may never happen, or applying all of the information that is currently available, however imperfect that may be, and acting now to try to prevent resistance which we know dramatically increases the risk of death.

This is what patients and their doctors can consider doing now, based upon information currently available, to help prevent resistance and improve survival:

- Patients with an exon 9 mutation should be on a higher dose of imatinib, perhaps as much as 800 mg. This means that patients need to have their tissue tested for mutational status. In the absence of such a test we would submit that the physician should assume that the patient has this comparatively rare mutation and be treated accordingly.
- Patients with other mutations should be on a higher dose of imatinib, probably 600 mg. Patients prescribed a higher dose should begin at 400 mg and gradually escalate to a higher dose in order to minimize and tolerate the greater side-effects associated with a higher dose of imatinib.

The therapeutic threshold of imatinib seems to start at around 300 mg. In other words, this is the dose that patients seem to start responding. The current recommended starting dose of imatinib is 400 mg. There have been many reports that describe various mechanisms that lead to variability between patients. We have discussed what we believe to be some of the more important ones here. One day we may have a much better understanding of these factors and be able to optimize a dose or drug concentration for each patient. Until that time comes, a dose increase from 400 mg to 600 mg in those patients that tolerate it, might provide a safety factor to prevent resistance.

- Patients experiencing side-effects should be informed that side-effects often get better over time and should not prematurely be moved to loser doses of imatinib. In addition, substantial attempts should be made to manage side-effects medically prior to considering lowering the dose of imatinib.
- Patients should be educated about the need to take imatinib. A Novartis study of prescriptions filled in CML and GIST patients found that compliance to taking imatinib was only about 75 percent. In this study, 80 percent of the patients started at 400 mg and overall 25 percent of the prescribed imatinib was not taken[9].

Patients should consider requesting testing of imatinib blood levels. Determining an optimum imatinib blood level will probably require a well-designed clinical trial that examines multiple factors. For now, the best information (Demetri et al. 2008 GI ASCO) we have is preliminary and suggests that trough imatinib plasma levels should be above 1,110 ng/ml (see "GI symposium offers interesting abstracts", in the February 2008 LRG newsletter). Testing imatinib blood levels is currently available for GIST patients. See www.gleevecmonitor.com (check the FAQs area under the Overview menu for information about GIST for details about this program).

Other Factors that need Further Evaluation in a Research setting

There are likely other factors than those discussed so far that may in large part determine why one patient needs more drug than another patient (interpatient variability). Three probable ones are:

OCT-1 activity – A number of CML researchers have shown a strong link between the activity of the OCT-1 protein and response and survival in CML[10,11]. OCT-1 is a protein that "pumps" imatinib into the tumor cell. In some patients, this protein is more effective than in other patients. (See the February 2008 issue of the LRG newsletter for a detailed discussion of OCT-1 in CML).

AGP/Protein Binding – Alpha-1-acid glycoprotein (AGP) is one of the main proteins in the blood that drugs bind to. Higher than normal levels of AGP bind more imatinib. While the current belief is that this does not result in reduced levels of imatinib reaching the tumor, it does seem to affect imatinib blood level testing[12]. High levels of AGP may cause the imatinib blood levels to appear higher. The effect may be an inaccurate reading of imatinib levels in the blood.

"Imatinib levels may drop 30 to 40 percent over the course of the first year on imatinib."

Drug Clearance – Drug clearance refers to how fast a particular drug is removed from the body. Research into the pharmacokinetics of imatinib in GIST patients has suggested that imatinib blood levels drop over time[13]. In fact, imatinib levels may drop 30 to 40 percent over the course of the first year on imatinib. What happens to those patients that start at 400 mg/day and have a 30 to 40 percent reduction in imatinib levels? In theory, they receive a dose of imatinib equivalent to taking 240 mg to 280 mg/day.

What causes the reduction in imatinib blood levels over time? At least three different theories have been put forth that might explain this phenomenon:

• Imatinib clearance increases over time-possibly related to improved liver function[13] in other words, the body becomes more efficient at removing imatinib.

• Multi-drug resistance proteins are induced over time decreasing the transport of imatinib across the intestinal membrane[14] .

• Patient adherence to taking the drug falls off over time[9].

The practical problem that patients face is that one, two or all three of these theories could be correct with different implications. The first two items are out of the patient's control, but the third is not. If patient adherence was the primary cause of dropping imatinib levels, then only less adherent patients would have to be concerned; but if imatinib clearance increased or multidrug transport was the problem then all patients stand to be affected.

Monitoring imatinib blood levels over time would remove the question from the realm of the theoretical and place it into the realm of the practical. From the patient's point of view it would not matter which theory was correct; if drug levels were monitored and shown to drop, the imatinib dose could be raised to compensate.

In Conclusion:

As further research is performed, it may be possible to develop a better understanding of the factors involved in optimizing a dose or drug concentration for each patient. Until this is achieved, the LRG believes that a dose increase from 400 mg to 600 mg for those patients that tolerate it might provide a safety factor to prevent resistance.

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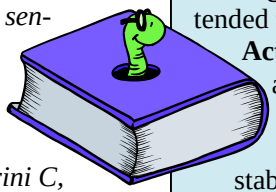

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Glossary

Starting Dose- Dose prescribed and intended to be taken.

Actual Dose- Dose delivered or actually taken. In the LRG study it is the dose being taken either at time of progression or, if the patient is stable, at the time of last examination.

Metastatic-this refers to the spread of the GIST tumor to another part of the body that is still part of the original tumor and not a completely new tumor.

Progression Free Survival (PFS) - Refers to the length of time during and after treatment in which a patient does not experience progression or recurrence.

Overall Survival (OS)-the patient is still living.

Hazard Ratio- Hazard is defined as the slope of the survival curve – a measure of how rapidly subjects are dying (or progressing if measuring PFS). The hazard ratio compares two treatments. If the hazard ratio is 2.0, then the rate of deaths (or progression) in one treatment group is twice the rate in the other group.

P Value- Tries to determine if there is a real difference between two groups. There is a chance that this difference is due to a coincidence of random sampling rather than due to a real difference between populations. Statistical calculations cannot tell you whether coincidence has occurred, but can tell you how rare this coincidence would be. P (probability) values are expressed as a decimal representing a percentage. A P value of 0.20 would indicate a 20 % chance of getting results with a difference as large as or larger than you observed.

Statistically Significant- Result is unlikely to have occurred by chance. Generally expressed with a P value that is predetermined (usually set so that P values below 0.05 are considered statistically significant).

Maximum Tolerated Dose (MTD)-The dose determined by a clinical trial as the highest dose able to be tolerated by most patients.

MetaGIST Project- Refers to the combined data of the phase III United States/ Canadian trial (S0033) and the phase III European/Australian trial(EORTC 62005).

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