First-Line Imatinib More Effective Than Widely Believed

Treatment for Resistant GIST - Improved, but Still Very Far to Go

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Most of us have heard this statistic: Gleevec works for about two years. Most of us have repeated it at one time or another. Of course, there have been some newer studies with patients that were probably less advanced than those in the early imatinib trials. These newer studies often show a somewhat longer time before patients progress on imatinib. Using LRG Patient Registry data, this report takes a fresh look at first line (1L) treatment as well as survival over multiple lines of treatment.

The statement that Gleevec works for about two years comes from the early trials for advanced GIST: the B2222 Phase II trial, and the two Phase III trials, U.S./North American (S0033) and Europe/Asia (EORTC 62005). In these three trials, the median progression-free survival (PFS) times varied from 19 to 24 months as shown in Table 1. This is often rounded off to give the “about 2 years” benefit, however, 22 months would probably be a more accurate number. For comparison, in the LRG Patient Registry, the median self-reported progression-free survival (srPFS) time is 31 months (Table 1).

The longer median srPFS time in the LRG Patient Registry might be influenced by different ways of measuring progression (self-reported versus strictly defined criteria) but it’s just as likely to represent the longer PFS times that come from including less advanced GIST patients, as has been reported in other studies. In either case, the 31-month LRG figure will serve as the baseline for further exploration of response to imatinib.

Table 1 – PFS comparison

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Pts.</th>
<th>Median PFS (mos.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B2222</td>
<td>147</td>
<td>24</td>
</tr>
<tr>
<td>S0033</td>
<td>746</td>
<td>19</td>
</tr>
<tr>
<td>EORTC</td>
<td>946</td>
<td>22</td>
</tr>
<tr>
<td>LRG</td>
<td>1034</td>
<td>31</td>
</tr>
</tbody>
</table>

Table 2 – Mutation types grouped by imatinib sensitivity

<table>
<thead>
<tr>
<th>Sensitive</th>
<th>Intermediate</th>
<th>Insensitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT exon 11</td>
<td>KIT exon 9</td>
<td>KIT/PDGFRA WT</td>
</tr>
<tr>
<td>KIT exon 13</td>
<td></td>
<td>D842V (PDGFRA)</td>
</tr>
<tr>
<td>PDGFRA exon 12</td>
<td></td>
<td>KIT exon 17</td>
</tr>
<tr>
<td>PDGFRA exon 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDGFRA exon 18, non-D842V</td>
<td></td>
<td></td>
</tr>
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The response of different mutation types to imatinib has been well described in the literature and will not be reviewed here. Using previous reports of sensitivity (that correlate well with LRG data), we grouped mutation types into three groups as shown in Table 2.

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The percentage of patients reporting a known mutation has increased over time and varies within different subgroups within the LRG Patient Registry. In patients being treated with imatinib for advanced GIST, 58.7% of patients have an unknown mutation. First-line (1L) srPFS for advanced GIST grouped by imatinib sensitivity is shown in Figure 1.

Patients with an unknown mutation have almost exactly the same srPFS time as when all four groups are combined (Figure 1 and Table 1). In other words, the Unknown Group is a very good surrogate for all patients combined (median srPFS 31.3 mo. and 31.0 mo. respectively). As such it actually becomes a distraction when looking at Figure 1. The mind tends to minimize the differences between the four survival curves.

If you take the Unknown patients out of the analysis (Figure 2-A) it becomes easier to focus on several things. First, the difference between the Imatinib-sensitive group and the other two remaining groups becomes quite obvious. Second, with the Unknown Group removed it now allows us to more clearly see the percentages that make up the three groups defined by imatinib sensitivity. The imatinib-sensitive group makes up two thirds (65.8%) of all patients and is dominated by those with a KIT exon 11 mutation which makes up 94% of the imatinib-sensitive group.

<table>
<thead>
<tr>
<th></th>
<th>Sensitive</th>
<th>Intermediate</th>
<th>Insensitive</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>281</td>
<td>67</td>
<td>79</td>
<td>607</td>
</tr>
<tr>
<td>Percent</td>
<td>27.2%</td>
<td>6.5%</td>
<td>7.6%</td>
<td>58.7%</td>
</tr>
<tr>
<td>Median srPFS</td>
<td>45.6</td>
<td>13.0</td>
<td>10.4</td>
<td>31.3</td>
</tr>
</tbody>
</table>

Figure 1 - 1L srPFS

Figure 2 - srPFS vs TTF

![Imatinib sensitivity](image)
Many patients experience significant benefit from imatinib after apparent progression. They may go on to a higher dose of imatinib, have surgery for a localized recurrence, or have slow progression.

If we use Time to Treatment Failure (TTF) instead of PFS, the total benefit of 1L imatinib for advanced GIST becomes clearer. For imatinib-sensitive GIST, the median TTF is 68.6 months. That’s three times longer than the 22 months PFS benefit reported if you take the median of the three pivotal GIST trials. This discrepancy is caused by three things:

• The 22-month figure lumps all patients together without considering imatinib-sensitivity.
• The patients in these early trials were probably more advanced than the typical patient diagnosed today.
• Total time on treatment is counted, not merely the time until progression.

For the 427 patients with a mutation test, the median TTF is 50.8 months, still 2.3 times longer than the PFS time typically cited as the expected benefit for 1L imatinib treatment. If we add in the 607 patients with an Unknown mutation, the median drops to 45.6 months for all 1034 patients with 1L treatment for advanced GIST. This is still about twice the length of time typically cited for PFS in the early trials.

For the KIT exon 9 patients who make up the entire Intermediate Group, the Intermediate curve moves closer to the Sensitive curve when TTF is considered. This is likely because, contrary to published guidelines, most KIT exon 9 patients are started on 400 mg and their dose is only escalated after progression. The difference between 13.0 months PFS and 34.3 months TTF is an increase of 163.9% compared to an increase of 50.4% for the Sensitive group and 51.0% for the Insensitive Group.

Both the srPFS and TTF times for the Insensitive group (n = 79) are longer than might be expected, 10.4 mo. and 15.7 mo. respectively. The reason for this is likely to be because 39 (49.4%) of these patients were Known or Likely SDH-deficient patients. Even in cases of no drug treatment, these patients often have varying rates of tumor growth including periods of stability, slow-growth, rapid growth and even shrinkage. For example, in a recently published LRG study, the srPFS time for 1L treatment for Known and Likely SDH-deficient patients was 14.7 mo. In contrast, srPFS for KIT exon 17 and PDGFRA D842V patients are each three months or less.

**Summary of 1L Treatment for Advanced GIST:**

Our conclusions from the 1L LRG data are:

• For imatinib-sensitive patients (Sensitive) 1L imatinib is more effective than widely believed.

• Patients should have mutational testing.

• Any discussion of expected imatinib benefit for patients about to start treatment should be individualized based on the patients imatinib-sensitivity which is based on mutational testing. This discussion should emphasize optimizing imatinib treatment for Sensitive and Intermediate patients to stay on imatinib for as long as possible.

The data presented here refers to advanced/metastatic patients; appropriately selected adjuvant patients (sensitive mutation, high risk of recurrence) can expect significantly greater benefit.

• Citing early trial data can be misleading, especially when it’s not put into proper context.
Treatment for Resistant GIST...Improved, but Still Very Far to Go

There is no doubt that the introduction of sunitinib and regorafenib has improved survival in GIST. The LRG recently published a study of LRG Registry patients demonstrating this.² For example, patients that began second line (2L) treatment before 2006 had a median overall survival (OS) time of 22.1 months compared to those that started 2L ≥ 2006 had a median OS of 34.9 months. This was, in large part, due to additional third line (3L) treatment options as more options became available over time with 2007 marking the start of options other than imatinib as 3L treatment.

It’s possible, perhaps likely, that two additional drugs (ripretinib and avapritinib) will be approved in the near future. If optimal treatment sequencing can be worked out, this may improve survival further. However, the median PFS times being reported ≥ fourth line (4L) for ripretinib (6.3 months) and for avapritinib (3.7 months) seem more like incremental improvement and not dramatic game-changing advances. The magnitude of the problem is shown in Figures 3 and 4.

As shown in Figure 3, there is a very large drop-off in survival from 1L for advanced GIST to 2L treatment. These survival times are calculated from all LRG Registry patients which includes those starting treatments as early as 2000 and those starting treatments as late as 2017. First-line adjuvant treatment is not shown on this graph. Three years of adjuvant imatinib has been shown to significantly increase Overall Survival.

A second visual representation of the problem can be seen in Figure 4 which shows living and deceased patients side by side in each treatment line. In the LRG Registry, 526 patients had or are on 2L treatment as of 2017. Of these, only 26% were still alive in 2017.
The data presented here emphasize two things: 1L Line treatment for imatinib-sensitive patients is better than widely believed and treatment for imatinib-resistant GIST, although improved, still leaves much to be desired. If approved, the addition of ripretinib and avapritinib to the GIST expert’s arsenal will be a welcome addition. However, it remains paramount to optimize 1L treatment. This includes mutational testing; optimal dosing, including imatinib plasma levels; side effect management, including long-term side effects; and optimizing adherence to taking medication.

It also raises many other questions. Is there anything else that can be added to imatinib to increase 1L line efficacy? Can a drug that is more effective and/or more tolerable than imatinib be developed? For at least two of the imatinib-insensitive mutation types, the answer appears to be yes. The introduction of avapritinib for patients with PDGFRA D842V and KIT exon 17 mutations is an example of remarkable progress for two of the imatinib-insensitive subgroups. With upfront mutational testing and appropriate drug selection, these two groups go from no treatment options to having an option that appears to be just as effective as imatinib for imatinib-sensitive patients.

References

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LRG Science is based on a foundation of Real World Evidence and Real World Data collected from: The LRG Patient Registry, SideEQ, Project Surveillance, and our collaborative efforts such as the Pediatric & SDH-Deficient GIST Consortium.

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A lot has been learned about the existence of more GIST subtypes and their relative susceptibility to first-line treatment with imatinib.

In this article Jerry Call and colleagues applied this new information to our Life Raft Group Patient Registry data about the efficacy of imatinib. They found, when doing so, that when imatinib is targeted only against those subtypes we now know to be susceptible to imatinib that progression-free survival was not two years as originally thought but over twice that.

This is clearly a testament to the importance of routinely incorporating mutational testing in the management of GIST treatment and a call to arms to make sure this in fact happens.

Norman J. Scherzer
Executive Director, The Life Raft Group

I am very impressed by the data presented in analysis of the GIST patient advocacy group, The Life Raft Group’s, “First-Line Imatinib More Effective Than Widely Believed: Treatment for Resistant GIST - Improved, but Still Very Far to Go” on the current results of therapy of advanced GIST. It is absolutely in line with the results presented based in our prospective Polish Clinical GIST Registry (established in 2001 and comprising about 1000 advanced patients treated with TKI due to metastatic disease and about 1800 localized cases treated surgically frontline) and data from a contemporary prospective trial (BFR14) from a French research group. Generally 1st line therapy results are much better that demonstrated in initial trial in the 2000s. According to current data, median progression-free survival (PFS) exceeds 3 years on 1st line imatinib therapy and median overall survival (OS) reaches 6 years. Good prognostic factors for longer OS were, among others, surgery of residual disease and the presence of exon 11 KIT mutations. Moreover, we have found a decrease of tumor burden at start of imatinib therapy over time. It is clear that evaluation of tumor mutational status should be obligatory in all metastatic/unresectable cases and also in patients who are candidates for adjuvant therapy. It guides the individualized therapy of patients. The other factor which may contribute to better results of first line therapy with imatinib in advanced GIST is surgical removal of residual disease which should be highly individualized and performed on the basis of a multidisciplinary decision in an expert center. Such a strategy might reduce the impact of initial tumor size and prevent secondary mutations, improving the long-term results of imatinib therapy.

Collecting real world data is very important for healthcare, it allows for additional analyses or confirmation of data from clinical trials. Based on our Registry data in multicenter collaboration we have developed nomograms of PFS/OS for patients treated with 1st line imatinib which are useful in clinical practice (Fig. 1). Our study confirmed also that current therapy of advanced GIST with tyrosine kinase inhibitors (both in 1st and 2nd line) in older patients achieves the similar disease control rate and final outcomes as in younger patients, but it demands the close cooperation of an experienced oncologist with patients for dose modifications and side effects management. The analyses of real world data in GIST lead to identification of new prognostic factors, such as blood neutrophil-to-lymphocyte ratio.

Therapy beyond imatinib is also related to better outcomes than reported from initial clinical trials but generally the results are not satisfactory, it is why new therapeutic options such as ripretinib or avapritinib are eagerly waited.

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Fig. 1. Prognostic nomograms for metastatic gastrointestinal stromal tumour treated with imatinib according to^4

### References


LRG Science is intended to highlight articles created by data collected from: The LRG Patient Registry, SideEQ, Project Surveillance, and our collaborative efforts, such as the Pediatric & SDH-Deficient GIST Consortium. It will also include content and commentary from GIST experts, case studies, editorials on vital issues and breaking news. LRG Science is based on a foundation of Real World Evidence and Real World Data.

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