Outcome of Advanced Gastrointestinal Stromal Tumor (GIST) Patients Treated With Imatinib Mesylate: Four-Year Follow-Up of a Phase II Randomized Trial

C. D. Blanke[1], H. Joensuu[2], G. D. Demetri[3], M. C. Heinrich[1], B. Eisenberg[4], J. Fletcher[5], C. L. Corless[1], E. Wehrle[6], K. B. Sandau[7], M. von Mehren[8]

[1]Oregon Health and Sciences University, Portland, OR, USA [2]Helsinki University Central Hospital, Helsinki, Finland [3]Dana Farber Cancer Institute, Boston, MA, USA [4]Norris Cotton Cancer Center, Lebanon, NH, USA [5]Brigham & Women's Hospital, Boston, MA, USA [6]Novartis Pharma AG, Basel, Switzerland [7]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA [8]Fox Chase Cancer Center, Philadelphia, PA, USA

ABSTRACT

Imatinib mesylate induces an objective response in the majority of pts with advanced, surgically incurable GIST, but secondary resistance and late relapses do occur. A phase II randomized clinical trial was previously presented (PASCO 20:1A, 2001; Combined GI Symposium 2:43, 2004), and data from an updated long-term analysis of this study are now available, with median f/u of 4.4 years. 147 pts were randomized to treatment with continuous imatinib, at 400 or 600 mg po daily. Two pts (1%) achieved a complete response, and 98 (67%) achieved a partial response (PR), for an overall objective response rate of 68% (95% CI 59.8-75.5). An additional 16% had prolonged stable disease. No significant response differences were seen between the two doses. Of the two pts who achieved complete responses, one died 3.2 years later without evidence of recurrence, having remained on imatinib until shortly before his death. The latter pt did not achieve a CR until he had been on drug for 3.5 years, and he remains in remission at 3.8 years. KIT and/or PDGFRA mutational status were highly significant in predicting response. Pts with an exon 11 KIT mutation had a PR rate of 87%, while those with an exon 9 mutation had a PR rate of 48%. Those with no detectable mutation of KIT or PDGFRA had a response rate of 0%. Overall, median time to response was 13 weeks*, median duration of response was 118 weeks, median time to treatment failure was 84 weeks, and median survival was 4.8 years (median not attained for pts with exon 11 mutations). Overall, 40%† have died of progressive disease. While secondary resistance and late progression can be seen in GIST pts treated with imatinib, many continue to benefit from drug therapy for a prolonged time, and responses can evolve over an extended treatment period. In particular, pts with exon 11 KIT mutations (the most common exon affected) have very high response rates and superior survival.

*Kaplan Meier estimate.
†The submitted abstract mistakenly stated that 63% have died of PD. The correct value is 40%. Please correct this in your abstract book.

INTRODUCTION

- GISTs are the most common mesenchymal tumor of the gastrointestinal tract
  — US annual incidence: ~ 5,000 cases
- GISTs are usually characterized by activating mutations of the tyrosine kinase KIT or PDGFR
- Imatinib mesylate, a selective inhibitor of the BCR-ABL, KIT, and PDGFR tyrosine kinases,is highly effective in advanced GIST
- Long-term benefit of imatinib in GISTs has been unknown

PATIENT SELECTION

- Pathologically confirmed, unresectable, or metastatic GIST
- Immunohistochemical documentation of KIT (CD117) expression
- Measurable disease with at least 1 tumor not previously treated with radiation therapy or embolization
- Previous chemotherapy (up to 4 weeks before entry), radiotherapy, surgery, or radiotherapy plus surgery were permitted
- Eastern Cooperative Oncology Group (ECOG) performance score of 0-2 (later modified to 3)

STUDY DESIGN

- Primary objective: Tumor response, based on conventional bidimensional Southwest Oncology (SWOG) criteria (categories: complete response [CR], partial response [PR], stable disease [SD], or progressive disease [PD])
- Secondary objectives: Time to treatment response, duration of response, and overall survival; safety assessments, graded according to National Cancer Institute Common Toxicity Criteria, were collected only during the 3-year core study
- The following data are based on a median follow-up of 52 months (range, 9.6-59 months), updated through May 13, 2005. The overall objective response rate (CR/PR) is presented with the 95% confidence interval. Time to event outcome, overall survival, and time to response were analyzed using Kaplan-Meier estimates; *P* values were derived by the log-rank test
- Figure 1 provides details on patient numbers, randomization, and treatment groups

RESULTS

Efficacy Results

Figure 1. Study Design

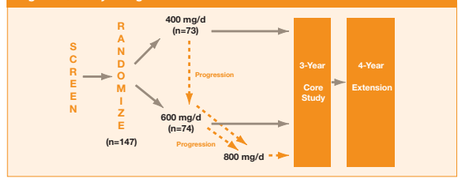


Table 1. Best Response

	400 mg N=73 n (%)	600 mg N=74 n (%)	All Patients N=147 n (%)
Complete Response	0	2 (2.7)	**2 (1.4)**
Partial Response	50 (68.5)	48 (64.9)	**98 (66.7)**
Stable Disease	10 (13.7)	13 (17.6)	**23 (15.6)**
Progression	11 (15.1)	6 (8.1)	**17 (11.6)**
Not Evaluable or Unknown	2 (2.7)	5 (6.8)	**7 (4.8)**

Table 2. Time to Response*

	Time to Response in 100 pts with CR/PR (weeks)
Mean	18
Min	3
Median (50%)	**12**
75%	**23**
Max	171

*Analysis based on proc univariate
No significant differences between the two treatment groups

Figure 2. Duration of Responses (Kaplan-Meier Estimate)

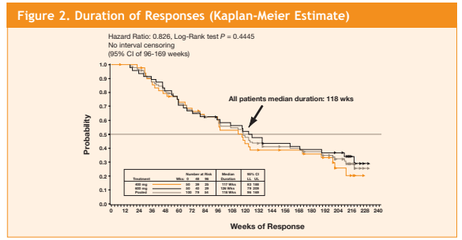


Figure 3. Overall Survival (Kaplan-Meier Estimate)

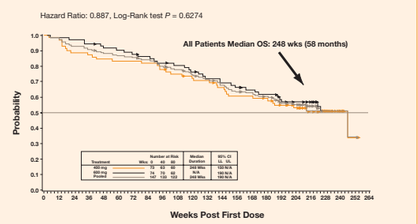
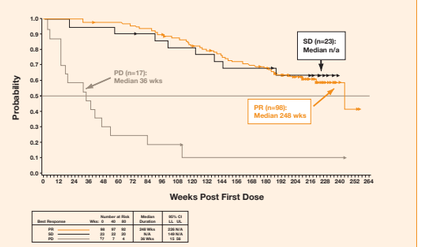


Table 3. Number of Deaths

	N (%)
Total # of deaths	67 (46%)
Reason for death	
Tumor progression	59 (40%)*
Other/unknown	8 (5%)

Total number of patients: N=147 (100%)
No significant differences between the two treatment groups
*The submitted abstract mistakenly stated that 63% have died of PD. The correct value is 40%. Please correct this in your abstract book.

Figure 4. Overall Survival by Best Response (Kaplan-Meier Estimate)



CR (n=2; median OS n/a) and Unknown/NE (n=7; median OS 144 wks) were taken out for display reasons

Mutational Results

Figure 5. *KIT* and *PDGFRA* Mutations

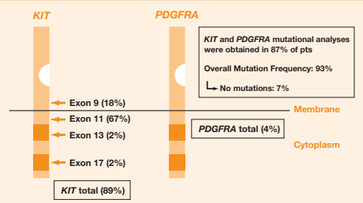
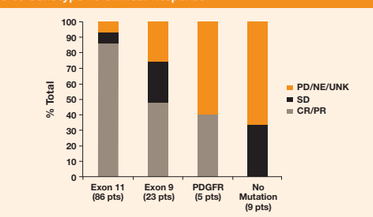


Figure 6. Genotype vs Clinical Response



Three patients had *PDGFR* mutations that are considered imatinib sensitive. Two of them had PR and 1 patient showed PD. Two patients had *PDGFR* resistant mutations and both patients exhibited PD.

Figure 7. Overall Survival by Genotype (Kaplan-Meier Estimate)

Median Survival	
No Mut.	250 days (36 wks)
Exon 9	1347 days (192 wks)
Exon 11	Not reached

Safety Results

Table 4. Most Common Grade 3/4 Adverse Events*

AE Grade 3/4	400 mg N=73 (%)	600 mg N=74 (%)	All pts. N=147 (%)
Fluid Retention	6.8	12.2	**9.5**
Abdominal Pain	12.3	5.4	**8.8**
Any Hemorrhage	5.5	10.8	**8.2**
Liver Toxicity	5.5	8.1	**6.8**
Diarrhea	2.7	6.8	**4.8**
Nausea	5.5	4.1	**4.8**
Operations	5.5	4.1	**4.8**
Vomiting	2.7	5.4	**4.1**
Musculoskeletal Pain	5.5	1.4	**3.4**

*Based on final analysis of the STI B2222 core study (median follow-up of 41 months)

CONCLUSIONS

- Imatinib mesylate is confirmed as highly effective therapy for patients with advanced metastatic or unresectable GIST
- Imatinib has an acceptable safety profile in patients with incurable GIST
- No significant differences were seen in the two imatinib dose groups (400 vs 600 mg)
- Although median onset of response is relatively fast with 12 weeks, 25% of patients achieved their response after 23 weeks
- Late responses are often seen in patients with initial SD
- Compared to historical data (Dematteo RP et al. Clinical management of gastrointestinal stromal tumor: before and after STI571. *Hum Pathol*. 2002;33:466-477), imatinib significantly changed the outcome of GIST patients with a current median overall survival of 248 weeks (58 months) versus approximately 15 months with chemotherapy
- Patients with SD or PR had a similar survival rate suggesting that these SWOG response categories may be associated with similar clinical benefit
- Tumor kinase genotype is predictive of clinical response to imatinib. In particular, patients with *KIT* mutations in exon 11 (the most common exon affected) have very high response rates and favorable long-term survival
- While late progression can be seen, the majority of patients derive benefit from imatinib treatment and responses in general are usually of lasting duration