# ASCO 2009 News

## Advanced GIST patients

Title: *Sorafenib fourth-line treatment in imatinib-, sunitinib-, and nilotinib-resistant metastatic GIST*
Author: Peter Reichardt, MD, HELIOS Klinikum, Bad Saarow, Germany
Abstract #: 10564

Dr. Peter Reichardt presented a retrospective study wherein Sorafenib showed significant clinical activity in resistant metastatic GIST patients. The clinical data of 32 patients who had successively failed imatinib, sunitinib and nilotinib were reviewed for outcome subsequent to fourth line sorafenib therapy. Clinical benefit was observed in 75 percent of the cases including seven partial responses and 17 achieving stable disease.

Median progression-free survival was reported as 5.7 months. This data is in line with data presented at the 2008 American Society of Clinical Oncologists conference (ASCO) from the Phase II sorafenib trial at the University of Chicago. Patients in that trial were resistant to either imatinib or imatinib and sunitinib. Data showing response by mutation is still under development at both centers. We have heard unofficially from more than one source that a phase III trial of sorafenib in GIST is on the drawing board.

Title: *In vitro activity of sorafenib against imatinib- and sunitinib-resistant kinase mutations*
Presenter: Jonathan Fletcher, MD, Brigham and Women's Hospital, Boston, MA (substituting for Mike Heinrich, MD OHSU). Both Fletcher and Heinrich are members of the LRG Research Team.
Abstract #: 10500

Dr. Jonathan Fletcher presented results showing that sorafenib has superior in vitro potency compared with imatinib or sunitinib against a panel of GIST-relevant mutant kinase cell lines and models. They found that unlike sunitinib, sorafenib is active against most imatinib-resistant secondary mutations involving the KIT activation loop (exon 17). In their abstract, Fletcher and Heinrich suggest that sorafenib should be evaluated for clinical efficacy as a second-line treatment for GIST with a primary KIT exon 11 mutation that has become resistant to imatinib.

This research is funded in part by The Life Raft Group and the GIST Cancer Research Fund and results from collaboration between Oregon Health & Science University and Brigham and Women's Hospital.

Title: *Phase I evaluation of SF1126, a vascular targeted PI3K inhibitor, administered twice weekly IV*
Author: E. Gabriela Chiorean, MD, Indiana University Simon Cancer Center, Indianapolis, IN
Abstract #: 2558

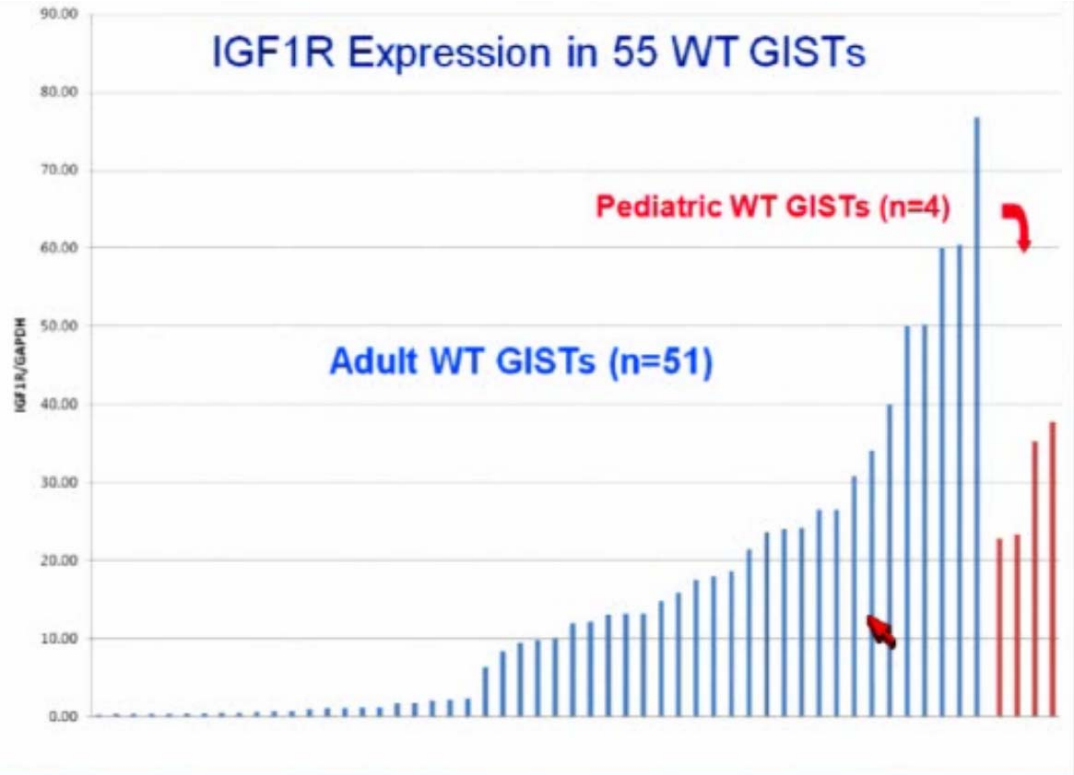
Four GIST patients have entered this Phase 1 trial of PI3K inhibitor SF1126. Preliminary results presented show that three had stable disease lasting from eight to 20 weeks. Additionally, it was reported that so far SF1126 has been well-tolerated and that there have been no clinically significant changes reported in glucose or insulin levels. This is important since PI3K inhibitors can have off-target effects on glucose metabolism.

This data is preliminary since the study is ongoing and still accepting patients. This trial would be a good choice for patients failing imatinib and sunitinib and in need of alternatives to off-label options. Chiorean also expressed interest in a Phase 2 study of this drug in GIST.

## Pediatric and Wildtype GIST patients

Title: *Evaluation of the presence of IGF1R over expression in wildtype and kinase mutant GI stromal tumors*
Presenter: Christopher Corless, MD, PhD, Oregon Health & Science University. Chris is a member of the LRG Research Team.
Abstract #: 10506

Fifteen percent of adult patients and 90 percent of pediatric patients have wildtype GIST. Corless presented data showing a wide degree of expression in IGF-1R levels in 114 patients with various GIST mutations including 51 wildtype cases. IGF-1R was not expressed at high levels in patients with exon 11, PDGFRA or other GIST mutations. It was expressed at high levels (30 times higher) in Pediatric wildtype GIST tumors and in a subset (60%) of wildtype adult tumors. Interestingly, about 40 percent of adult wildtype tumors show low expression levels typical of KIT/PDGFRA mutant GIST. In addition, there was a subset of tumors with varying mutations that had low expression levels of KIT, PDGFRA and IGF-1R.




Corless commented, “It is quite a heterogeneous mix. It implies a lot more biology going on than we had previously appreciated.” (*Editorial:* In context this comment conveys the importance of wildtype tumors in discovering the diverse biology of GIST beyond KIT. The answers provided through study of wildtype tumors could eventually impact all GIST patients who face resistance. It also points out the need for wildtype tissue in a shared resource, like the LRG Tissue Bank, where **all GIST researchers** have access.)

In a clinical response analysis on a subset of 24 Phase III imatinib trial wildtype tumors the sample size was small but the numbers were “tantalizing”. Corless reported that there was an observable (but not yet significant) “trend” between high IGF-1R expression and less favorable response on imatinib. In these same tumors, high KIT expression was significantly correlated with good response to imatinib. This study adds to work done earlier by Dr. Cristina Antonescu at Memorial Sloan-Kettering Cancer Center (MSKCC) and Dr. Andrew Godwin at Fox Chase Cancer Center. An IGF-1R inhibitor is not yet approved, but multiple candidates are in trials worldwide. Corless anticipates that as these studies get underway, additional data will further clarify these trends.

## Newly diagnosed GIST patients

Title: *Masatinib mesylate in imatinib-naive locally advanced or metastatic gastrointestinal stromal tumor*
Presenter: Axel Le Cesne, MD, Institut Gustave Roussy, Villejuif, France;
Abstract #: 10507

Thirty patients are reported in this Phase II trial analysis. Results indicate a favorable comparison with imatinib as a first-line treatment for GIST. The definitive answers regarding this drug should come from the Phase III first-line study of masatinib versus imatinib which is now recruiting in the United States and Europe. It was reported that one patient with a PDGFRa D842V mutation had prolonged stable disease and was able to achieve surgical remission. Also reported were earlier results of in vitro tests that show masatinib is two to three times more effective against GIST exon 9, 13 and PDGFRa mutations in a cell proliferation assay. These mutations are less frequent but are often the source of primary resistance to imatinib.

Because of the small patient population (30) in this study (which is compared to the Phase III U.S. and European studies of 694 and 946 patients taking imatinib) the results have to be viewed with caution. For example, the 95 percent confidence interval of the reported 60 percent two year progression-free survival was 38 percent to 76 percent. Also, the mutation analysis is partial (15 patients available) and indicates a preponderance of exon 11 and no exon 9. (A preponderance of exon 11 would improve the comparative results since exon 11 patients are historically the best responders to this type of TKI) This highlights the issue of selection bias that can potentially occur in GIST studies where mutation analysis is not complete.

In an interesting aside, Dr. Le Cesne reported metabolic response was more accurately analyzed using Dynamic Contrast Enhanced Ultra-Sound (DCE-US) imaging versus PET.

Comparison of Masitinib vs. Imatinib in first line treatment for GIST*

| | Masitinib | Imatinib |
|---|---|---|
| Tolerability | Good | Good |
| Complete response + Partial Response | 53% | 45% |
| PFS @ 6 months | 80-90% | 80-90% |
| PFS@ 2 years | 60% (37-76%) | 41%[1] (36%-47%) Blanke CD et al J Clin Oncol 2008;26:626 |

*Casali, Le Cesne, ASCO 2009

NOTE: Comparisons of different trials must be viewed with caution, especially those involving relatively small numbers.

- Other imatinib trials have shown imatinib PFS rates as high as approximately 50% at two years

# All GIST patients

Title: *Analysis of an observational registry of gastrointestinal stromal tumor (GIST) patients*

Author: Peter Pisters, MD, University of Texas M.D. Anderson Cancer Center, Houston, TX

Abstract #: 10557

This poster reported the latest data from the GIST ReGISTry, an online database of GIST patient statistics maintained by a group of American and Canadian GIST specialists and supported by Novartis Pharmaceuticals. The most recent data represents 882 GIST patient profiles collected as of March 30, 2009. Conclusions reported include:

- Mutation analysis is infrequent with about six percent overall; 1.4 percent in the community oncology practice setting and 12 percent in the university cancer center setting in the United States. In the sister "GOLD ReGISTry", which covers non-U.S. sites, and which was last reported at ASCO GI (Gastrointestinal) in January 2009, 84 of 500 patients (17%) had initial mutational testing and 40 percent of sites in the study reported use of mutational testing for GIST. This may reflect both the higher percentage of university sites and the higher proportion of advanced GIST patients in the GOLD ReGISTry.

- Clinical trial participation is infrequent.

- Adjuvant use of imatinib is increasing and now includes 17 percent of patients in the registry

Title: *Myelodysplastic syndromes developing after imatinib therapy for GIST*
Author: P. Spadaro, MD, Casa di Cura Villa Salus, Messina, Italy
Abstract #: 10532

In a prospective study of 49 GIST patients the authors conclude that during imatinib therapy some patients with GIST develop chromosomal abnormalities and that although rare these findings highlight the need for monitoring GIST patients treated with imatinib.

A series of 49 patients were given bone marrow biopsies and blood tests before and after starting imatinib therapy in 2007 and 2008. 15 patients developed grade 3 or 4 low red cell or white cell counts while on imatinib. On microscopic analysis of bone marrow cells, eight patients (16%) showed some form of chromosomal abnormality. Of these, four were intermittent and not clinically significant; three were associated with a chronic low blood-count condition and one developed into Acute Myeloid Leukemia (AML). Although this study was not designed to answer the question, the authors speculate that imatinib may be the cause of the chromosomal abnormalities.

Title: *Gastrointestinal stromal tumor associated with other primaries: A study of 154 patients*
Author: Renganayaki K. Pandurengan, MD Department of Epidemiology, University of Texas M. D. Anderson Cancer Center, Houston, TX

Abstract #: 10567

In a retrospective study of GIST patients treated at MD Anderson Cancer Center from 1995 through 2007, 153 of 783 (20 percent) patients were identified as having a primary cancer in addition to GIST. Although they did not include a comparison with a similar population without GIST, the authors report that the occurrence of other malignancies appears to be more common than expected. In their conclusions they state that surveillance (for other cancers) is an important component of GIST management.

The 20 percent coincidence rate observed here is within the range of other studies of secondary cancer in GIST patients (4.5% - 33%). The most common second cancers occurring in this population in percentage terms of the 153 total cancers were:

- Genitourinary Carcinoma-62
  High runners included in this total were
  - Prostate-28
  - Kidney-12

- Gastrointestinal Carcinoma-48
  High runners included in this total were
  - Colorectal-17,
  - Esophagus-10
  - Pancreas-6

Other major cancers mentioned were:

- Breast-15
- Leukemia/Lymphoma-12
- Head, Neck and Lung-11
- Other sarcomas-9
- Melanoma-9
- Thyroid-6
- Endocrine-3
- Neurologic-1
- Unknown primary-10

These numbers add up to186, reflecting the fact that some patients had multiple additional cancers. Higher percentages of GI carcinoma and lower percentages of prostate cancer were observed in a larger (4,813 GIST patients) and earlier review study.