

Gastrointestinal Stromal Tumors (GIST) Clinical Trials Planning Meeting

Executive Summary

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The design and execution of clinical GIST research is difficult due to the extraordinary efficacy of first-line therapy with imatinib mesylate, as well as subsequent salvage therapy. Members of the GIST Task Force plus other experts in the field met on April 16, 2009 to discuss potential trial designs (specifically, appropriate endpoints for GIST studies) and related issues.

Adjuvant treatment of GIST

A major topic of discussion was the issue of curing a patient versus controlling a patient's disease long-term. A patient is not technically cured if discontinuation of adjuvant therapy results in relapse. GIST is relatively unique versus other types of cancers in that being disease-free for several months or even years beyond surgery for GIST does not rule out later relapse. Although few patients to date have relapsed on continuous long-term adjuvant imatinib, some patients simply discontinue imatinib use due to financial or other personal reasons. Additionally, because salvage treatment is highly effective in GIST, some patients may be less motivated to remain on imatinib indefinitely. Adding to the difficulty in conducting adjuvant GIST trials is the fact that many patients receive surgery and imatinib in the community setting prior to being given the opportunity to participate in a clinical trial.

There was general agreement among the attendees that relapse-free survival (RFS) would be an appropriate primary endpoint for an adjuvant trial. However, RFS is not necessarily a surrogate for overall survival (OS) in GIST and should be interpreted as a stand-alone endpoint.

The main question of interest in the adjuvant treatment of GIST is: if one year of adjuvant imatinib therapy is not sufficient to cure GIST, what duration of treatment might be sufficient?

A proposed trial will provide information comparing five years of treatment with one year of treatment. Because no extremely attractive adjuvant trial designs were presented at the Clinical Trials Planning Meeting, it was decided that it would be preferable to obtain duration data from this imminent trial; this approach would also conserve resources for more attractive studies in the future. A possible future trial design would involve randomization of patients after 5 years of adjuvant imatinib therapy to either discontinue imatinib therapy or continue therapy indefinitely.

Metastatic disease

The main competition to metastatic treatment trials is treatment of patients in the community setting. This is particularly true for patients with an initial diagnosis of metastatic disease in whom community oncologists are comfortable starting first-line imatinib and for patients with progression on imatinib in whom community oncologists are comfortable starting second-line sunitinib. For a metastatic trial to be successful, it

must have an exciting design for which patients are willing to travel to academic centers from their more conveniently located community center. Furthermore, community oncologists must be aware of ongoing trials so that eligible patients can be offered participation. It was agreed that both progression-free survival (PFS) and OS are generally appropriate endpoints for metastatic trials.

The Southwest Oncology Group (SWOG) is currently conducting a phase III trial (imatinib +/- bevacizumab) in metastatic GIST patients. Although three other cooperative groups have formally endorsed the trial, accrual has been well below the targeted rate and the trial may close due to failure to achieve the NCI's critical target of 20% of total projected accrual by quarter six. It was proposed that the trial be redesigned as a single arm phase II trial of imatinib + bevacizumab. Such a design would attempt to improve on the 66% response rate of single-agent imatinib and aim for an increase in median PFS from 18 months to 27 months. For future trials in metastatic disease, it will be critical that there is strong early phase clinical data (and not just strong theoretical rationale) for agents or combinations of agents being compared to imatinib.

Other proposed designs in metastatic disease:

- 1) Fox Chase: IGF-1R ab +/- anti KIT agent (any-line)
- 2) U. Chicago: third line phase II or III trial of sorafenib vs. imatinib in imatinib- and sunitinib- resistant patients (imatinib started at previous highest dose)

Design of GIST surgical trial

The GI Steering Committee suggested consideration of an alternate primary endpoint for a recently proposed GIST surgical trial (Cancer and Leukemia Group B 140802), a randomized phase III study examining imatinib therapy +/- early surgical resection for resectable metastatic GIST. The concept attempts to determine whether early surgery leads to longer disease control compared to continuing imatinib with the option to offer surgery upon progression.

Rather than the originally proposed primary endpoint of PFS, it was agreed that "time to change in systemic therapy" would be feasible as a primary endpoint. The events that would qualify as a change in systemic therapy would include an increase in imatinib dose or a switch to sunitinib. If surgery (either initial surgery or a subsequent operation) allows a patient to remain on the initial dose of imatinib, this would NOT be considered a change in systemic therapy; this criteria would hold true for both arms.

In an attempt to compensate for the lack of background data on this endpoint (specifically the difficulty in determining the expected value in the control arm), data regarding "duration of protocol treatment" from the S0033 trial will be used as a surrogate for "time to change in systemic therapy".

The proposed design for the revised CALGB surgical trial will include the following specifications:

- 1) median time to change in systemic therapy in control arm: 24 months
- 2) goal in surgery arm: 43.2 months
- 3) accrual rate: 5-6 evaluable patients per month (total accrual 238)

- 4) 39.5 months of accrual with 18 additional months of follow-up

It was agreed that the trial would need to be conducted in a small number of specialty centers. An excellent communication strategy will be critical in achieving surgical quality control and acquiring strong support from the medical oncology community; it was felt that, even with a dedicated core group of surgeons, buy-in from the medical oncology community will be crucial to the success of the trial. A system for reviewing scans centrally is also being considered. A revised concept will be submitted to the GIST Task Force and ultimately the NCI Gastrointestinal Cancer Steering Committee.

Correlative science in GIST

The Task Force would like to mandate tissue submission in all cooperative group GIST trials. Because of the rarity of this disease and the limited number of patients, collection of as many high-quality tissue samples as possible is desirable; a well-defined collection and submission system is needed to maximize the utility of the limited resources. One item that will require further discussion is the fact that many local IRBs require knowledge of the intended use of tissue samples in order to approve the mandating of specimen collection.