FOLLOW-UP IN LOW RISK GASTROINTESTINAL STROMAL TUMORS (GISTs) – RETROSPECTIVE ANALYSIS OF CLINICAL FEATURES AND OUTCOMES

Title:	Follow-up in low risk Gastrointestinal Stromal Tumors (GISTs)- Retrospective analysis of clinical features and oucomes
Study Code:	ISG-RetroGIST-LR
NCT number:	NCT04599660
Sponsor's Name and Address:	I.S.G. Italian Sarcoma Group
Sponsor's Telephone Number:	Tel +39/051/014.59.78
Study Version/Date:	Version 1.0 of 01 June 2020
Type:	**No Profit** *(in compliance with Italian DM 17/12/2004)*
Metodology	Observational retrospective
Study Clinician	Dr. Giovanni Grignani IRCCS Candiolo
Study Authors	Giovanni Grignani
Funding:	None

PROTOCOL SIGNATURES PAGE

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Sponsor Protocol Code: ISG-RetroGIST

Protocol Version: 1.0

Protocol Date: 23 01 June 2020

Sponsor and author approval:
This clinical study protocol has been reviewed and approved by a sponsor representative, and the co-investigators, listed below.

Sponsor Signature:
Piero Picci, MD

Study Clinician signature:
Giovanni Grignani, MD

I have read the contents of this protocol and agree to abide by all provisions set for therein.
I agree to personally conduct or supervise this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki and with the International Conference on Harmonisation guidelines on Good Clinical Practice (ICH E6), and applicable Italian regulatory requirements.
I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. I agree to make available to sponsor personnel, their representatives and relevant regulatory authorities, my subject's study records in order to verify the data that I have entered into the case report forms.

Site…….
Principal
Investigator……
Signature……...

AMENDAMENT AND MODIFICATION

Date	Type of amendment	Protocol Version	Summary of changes	Pages
None				

Background

In the field of soft tissue sarcomas, Gastrointestinal Stromal Tumors (GIST) represents a really peculiar neoplasm for its biological and clinical properties. Surgery (if feasible) is the main therapeutic approach for all the patients with localized disease, while a pharmacological adjuvant treatment is reserved to those with a relevant risk of recurrence/progression.

After tumor removal, clinical and radiological follow-up is of central importance to early intercept recurrence and to evaluate the most correct subsequent therapeutic approach. In particular, for the group of patients with GIST at very-low and low risk of recurrence/progression, the evidences to support a specific follow-up program and its features are poor.

Description of the project and of the population on study

On the basis of the aforementioned considerations, we propose a multi-institutional retrospective study in order to identify the most relevant and advisable features of follow-up, and to explore its impact on principal clinical outcomes. Moreover, a dedicated effort will be pursued to identify the peculiar characteristics (if any) of patients that experienced recurrence of the disease.

We will collect data about patients affected by primary GIST at very-low and low risk of recurrence/progression, referred to participating Institutions between January 2000 and February 2020.

Inclusion criteria*:*

- >18 years at diagnosis
- primary GIST removed by surgery or endoscopic procedures
- availability of medical data needed for the study
- very-low and low risk GIST defined as:

  - largest size of < 3 cm (for all sites of origin)
  - gastric GIST with ≤ 5/50 HPF mitoses **and** ≤ 10 cm in the largest size
  - gastric GIST with > 5/50 HPF mitoses **and** ≤ 5 cm in the largest size
  - intestinal GIST with ≤ 5/50 HPF mitoses **and** ≤ 5 cm in the largest size

Exclusion criteria:

- Metastases at diagnosis.
- Previous treatment with imatinib

Primary objectives

1) To describe the most relevant features (focusing on type of exams and timing) of follow-up in very-low and low risk GIST patients included.

Secondary objectives

1) To assess baseline clinical and disease-specific factors with possible impact on survival analyses.
2) To perform analyses of recurrence-free survival (RFS), post-recurrence progression-free survival (PR-PFS), disease-specific survival (DSS) and overall survival (OS).
3) Subgroup analyses according to mutational status and histological characteristics depending on sample size at time of primary analysis.
4) To explore the possible impact of GIST follow-up on the detection and prognosis of second tumors.

Methods

We will retrospectively collect demographic, clinical, surgical, pathological and molecular characteristics. Furthermore, we will collect the main features of follow-up, recurrence and survival data. In addition, we will register other neoplasms detected before, after or concomitantly to the diagnosis of GIST.

Participating Centers will be asked to fill in a common dataset. Patients' data will be entered in a de-identified fashion. This file will be centralized at the PI's Institution. Then, participating Centers will be queried for missing or incomplete data. Participation to study will be possible upon local IRB approval and data transfer agreement with PI's Institution.

Statistical Considerations

Statistics will be performed at IRCCS Candiolo Cancer Institute.

Descriptive statistics will be used to summarize all patients' characteristics. Data will also be displayed graphically, whenever appropriate. Qualitative variables will be compared using the χ^2 and Fisher's exact tests where indicated. Differences of proportions will be computed assuming a normal distribution. A *p*-value ≤ 0.05 will be considered statistically significant. All survival endpoints will be computed according to the Kaplan-Meier method and compared by the two-sided log-rank test if indicated (both stratified and unstratified). The hazard ratio (HR) estimates for each factor will be calculated with Cox regression. Qualitative variables will be compared using the $\chi 2$ and Fisher's exact tests and/or the Mantel-Haenszel odds ratio (OR) estimates. For multivariate analyses the Cox proportional hazards model will be employed. When indicated, tests will be two-sided and results will be reported with 95% confidence intervals (95%CI) or interquartile ranges (IQR).

Enrollment Procedure

Patients considered eligible will be included in the study, after providing a written informed consent.

Data collection

Clinical data will be retrieved by patient medical charts.

A protocol-specific CRF reporting the results of the review will be provided.

A CRF is required and should be completed for each included subject.

Ethics and Quality Assurance

The clinical trial protocol and its documents will be sent before initiating the study to the competent Authority and Ethics Committees of each participating site for its approval.

The responsible investigator will ensure that this study is conducted in agreement with either the most updated Declaration of Helsinki and all the laws that apply to clinical study and to patient protection.

The protocol has been written, and the study will be conducted according to the principles of the ICH Harmonized Tripartite Guideline for Good Clinical Practice

(ref: http://www.emea.eu.int/pdfs/human/ich/013595en.pdf).

Informed Consent

All patients will be informed, by the investigator, of the aims of the study, the possible risks and benefits that will derive from the study participation.

The Investigator must clearly inform that the patient is free to refuse participation in the study and that can withdraw consent at any time and for any reason.

They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

The informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative".

The Investigator must also sign the Informed Consent form, and will keep the original at the site and a copy of the original must be handed to the patient.

The competent ethics committee for each Institution participating to the study must validate local informed consent documents before the study can be opened. It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the study whenever he/she wants. This will not prejudice the patient's subsequent care.

Confidentiality

In order to ensure confidentiality of clinical trial data as disposed the national and European applicable regulation, data will be only accessible for the trial Sponsor and its designees, for monitoring/auditing procedures, the Investigator and collaborators, the Ethics Committee of each corresponding site and the Health Authority.

Investigator and the Institution will allow access to data and source documentation for monitoring, auditing, Ethic Committee revision and inspections of Health Authority, but maintaining at all times subject personal data confidentiality as specified in the " EU General Data Protection Regulation 2016/679"

The Investigator must guarantee that patient anonymity is kept at all times and their identity must be protected from unauthorized persons and institutions.

All patients included in the study will be identified with a numeric code, so that no identifiable personal data will be collected (pseudo anonymization)

The Investigator must have and conserve a patients' inclusion registry where it figures the personal data of the patient: name, surname, address and corresponding identification code into the study, this register will be kept on the Investigator File.

Publication of results

The results from this study will be published or shown at scientific conferences. The final publication of the study results will be written by the Principal Investigator and will consider the contribution of the participant sites.

Sponsor Role and Responsibility

The sponsor is the sole owner of the data and is responsible of all the clinical trial activities from study design, development, data collection, management, analysis, and interpretation of data, writing and the decision to submit the report for publication written by the Principal Investigator.

Budget

No budget is planned.

References

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