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Patterns of Care and Outcomes of Patients With METAstatic Gastrointestinal Stromal Tumors (METAGIST)

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Title	**METAGIST** **Patterns of care and outcomes of patients with METAstatic GIST in a real-life setting: the METAGIST national observational study from the GSF-GETO**
Rational	Gastro intestinal stromal tumors (GIST) are rare mesenchymal tumors of the gastrointestinal tract characterized by somatic mutations in the gene encoding the KIT or the PDGFR alpha protein[1]. Treatment of localized forms relies on adequate surgery without tumor spillage and systemic treatment with imatinib according to risk of relapse defined by localization, tumor size and mitotic count, as well as mutational status. Advanced and relapsing forms are currently treated with oral tyrosine-kinase inhibitors (TKI) of KIT and PDGFR such as Imatinib, Sunitinib and Regorafenib[2,3]. Over two decades significant changes in drug discovery have impacted treatment strategies, notably via patient's access to various clinical trials. The use of focal treatments such as surgery or interventional radiology with mini invasive procedure of oligometastasis is also being proposed in some cases. There is no precise data on patterns of sequential treatments used, especially proportions of patients with metastatic GIST eventually benefiting from access to a clinical trial or a focal treatment strategy in the course of their disease, and their results in terms of survival on a real life national level. Using the French sarcoma Group national database we aim at describing treatments strategies proposed patients with metastatic GIST in the real life setting.
Objectives	**Primary objective** To describe clinic-biological profiles, patterns of care and modalities of treatment of patients with metastatic GIST in a real-life national setting. **Secondary objectives** - time to next treatment (TNT) - overall survival - proportion of patients included in a clinical trial during the course of their disease -

Material and Methods	**Inclusion** - patients ≥ 18 years old - with a diagnosis of **metastatic GIST** (metastatic at diagnostic or metastatic relapse) - From 1990 to 2018 - with histological review performed by members of the pathological sub-committee of the GSF-GETO - treated in one of the participating national reference network centers members of the GSF-GETO - included in the prospectively maintained database of the GSF-GETO: the ConticaGIST **Methods** Descriptive data (see SARCOMABCB DICTIONNARY) - Initial patients characteristics: age, gender, PS - tumor characteristics : date, histology, location, size, mitotic count, miettinien classification, mutational status - Initial treatment : initial surgery type, date, margins, tumor spillage, adjuvant systemic treatment (start and stop date) - Metastatic disease characteristics : date, PS, location of metastasis - Treatment in the metastatic setting : molecule used (start and stop date, best RECIST response), locoregional treatment performed, inclusion in a clinical trial - Latest status : date, patient lastest Status, tumor latest status Survival data - Time to next treatment (TNT) TNT defined as the time from the systemic treatment onset to the next treatment or death due to any cause, whichever came first. When neither death nor new systemic therapy is observed, TNT is censored at the date of last patient contact. - Overall survival in the metastatic setting (OS) defined as the interval between the diagnosis of metastatic disease or the first-line systemic therapy onset and the time of death. When death is not observed, OS is censored at the date of last patient contact.
Statistics	Statistical analysis of the baseline demographics and clinical outcomes will be based on all data available up to the cut-off date of December 31, 2018. Descriptive statistics will be used to show the distribution of variables in the population. Multivariate logistic regression models will be used to identify biological and clinical factors associated with the type of treatment received and with the probability of survival 5 years after the diagnosis of metastases. Follow-up times will be described as median values based on the inverse Kaplan–Meier estimator. Prognostic factors of TNT and OS will be identified using Cox proportional hazard models. The variables included in the univariate and multivariate analyses are the descriptive data.

	The correlation between TNT and OS will be evaluated at each of the four first-lines of metastatic chemotherapy by a Spearman rank correlation coefficient and expressed as a value between 0 (no association) and 1 (perfect association). We will use a reviewed copula-based approach that introduces an iterative multiple imputation method for the estimation of the correlation coefficient. The data will be analyzed using the SAS v9.3 and R v3.3 software packages.
Timeline	February 2019 : end of collection of data and updating of the conticaGIST March - April 2019 : first version statistical analyses
Ref	1. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science.* 1998;279(5350):577-580. 2. Buchdunger E, Zimmermann J, Mett H, et al. Inhibition of the Abl protein-tyrosine kinase in vitro and in vivo by a 2-phenylaminopyrimidine derivative. *Cancer Res.* 1996;56(1):100-104. 3. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet.* 2013;381(9863):295-302.