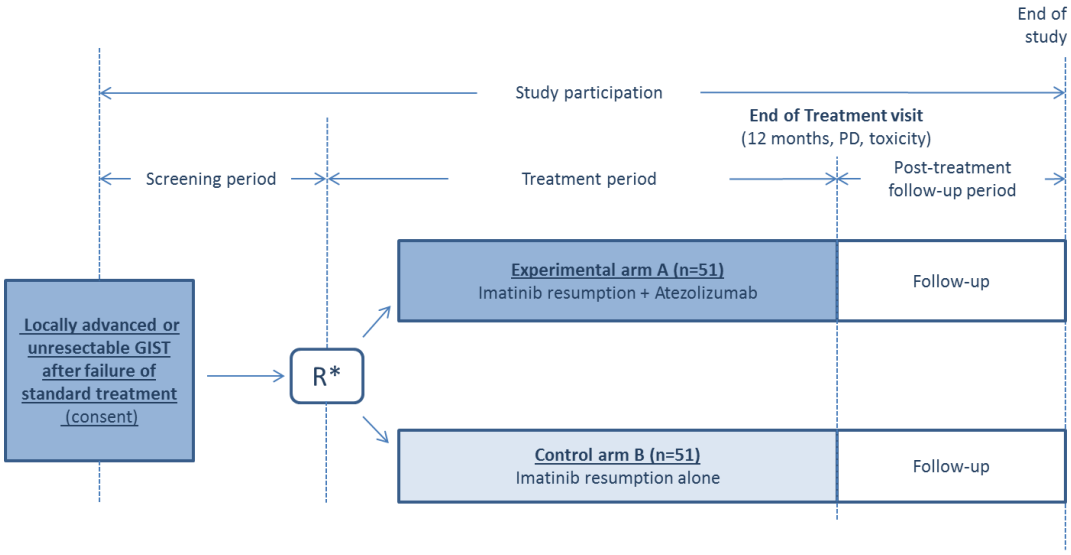
SYNOPSIS

Title	ATEZOGIST – A prospective, randomized, multicenter, comparative study of the efficacy of imatinib resumption combined with atezolizumab versus imatinib resumption alone in patients with unresectable advanced gastrointestinal stromal tumors (GIST) after failure of standard treatments
Sponsor	Centre Léon Bérard, Lyon, France
Study identification	Sponsor ID: ET19000075 EudraCT number: 2019-001547-43 NCT: to be determined
Version	1.0 dated April 5th 2019
Study coordination	Coordinating investigator **Dr Mehdi BRAHMI**, Centre Léon Bérard, Lyon Coordinating centre: Direction de la Recherche Clinique et de l'Innovation, Centre Léon Bérard, Lyon
Participating sites	10-15 participating sites of the French Sarcoma Group (GSF) are expected
Therapeutic indication	Patients with unresectable advanced GIST after failure of imatinib (disease progression) and sunitinib (either disease progression or intolerance).
Study objectives	**The primary objective is to compare the efficacy (Progression-Free Survival – PFS) of imatinib resumption combined with atezolizumab *versus* imatinib resumption alone** in patients with unresectable locally advanced or metastatic GIST after failure of standard treatments **Secondary objectives** • Best Response Rate (BRR), • Objective Response Rate (ORR) • Time to Treatment Failure (TTF) • Overall Survival (OS) • Quality of Life • Tolerance **Exploratory objectives** Overall response will also be assessed using the modified RECIST 1.1 for immune-based therapeutics named iRECIST: iPFS, iBRR and iORR. Any documented disease progression (iUPD (unconfirmed immune PD) according to iRECIST) for patients treated with imatinib combined to atezolizumab will be confirmed 4-6 weeks later (iCPD (confirmed immune PD)).
Study design	This is a prospective, randomized, multicenter, comparative study. A total of 102 patients with unresectable advanced GIST after failure of standard treatments (disease progression for imatinib and disease progression and/or intolerance for sunitinib), will be centrally randomized (1:1 ratio) in one of the study arms as described in the study scheme bellow.



* Randomization will be stratified according to:

- The number of previous treatment lines: 2 or >2
- The tumor KIT (exon 11) mutational status: wild type or mutated

Patients will be treated with imatinib associated with atezolizumab or not until the end of treatment visit at 12 months, unacceptable toxicity or willingness to stop, whichever occurs first. In the experimental arm, disease progression (according to RECIST V1.1), will be confirmed 4-6 weeks later using iRECIST recommendations. In agreement with these recommendations, patients who are clinically stable could continue on treatment until the next assessment (4-6 weeks later) and confirmation of disease progression.
Nota Bene : the first disease progression (according to standard RECIST 1.1) will be used for the study of the primary endpoint PFS.

The end of the study will be the Last Patient Last Visit, defined as the 90-day safety follow up visit of the last active patient.

Study population

Inclusion criteria

I1. Male or female ≥ 18 years at the day of consenting to the study;

I2. Patients must have histologically confirmed diagnosis of GIST (within the French Reference Network in Pathology of Sarcomas - RRePS network);
Nota Bene: mutational statuses and level of expression of PD1/PD-L1 will not be considered as selection criteria but will be studied as endpoints for translational objectives.

I3. Willingness to undergo fresh biopsies (baseline and relaspse);
Nota Bene: At baseline, if patient's archival tumour tissue has been collected after the last anti-cancer treatment, biopsy at baseline is not mandatory.

I4. Locally advanced or metastatic disease confirmed as measurable according to the RECIST V1.1 ;

I5. Patients who previously failed to at least imatinib then sunitinib. Failure is defined for Imatinib as progressive disease and for sunitinib as progressive disease and/or intolerance;
Nota Bene: Patients may have received a 3rd line with regorafenib or subsequent anticancer treatments

I6. Performance Status of the ECOG of 0 or 1;

I7. Adequate bone marrow and organ function defined by the following laboratory results:

a. Bone marrow:
   i. Hemoglobin ≥ 9.0 g/dl,
   ii. Absolute Neutrophils Count (ANC) ≥ 1.5 Gi/l,
   iii. Lymphocytes count ≥ 0.3 Gi/l,
   iv. Platelets ≥ 100 Gi/l;

b. Coagulation:
   i. Prothrombin time ≤ 1.5 x Upper Limit of the Normal (ULN) for patients without therapeutic anticoagulation.
   Patients with therapeutic anticoagulation must have stable dose of treatment.

c. Hepatic function:
   i. Total serum bilirubin ≤ 1.5 x ULN (except patients with Gilbert's syndrome who must have total serum bilirubin ≤ 3.0 x ULN),
   ii. Transaminases (ASAT/ALAT) and Alkaline Phosphatases ≤ 2.5 x ULN (or ≤ 5.0 x ULN in case of liver metastases),

d. Renal function:
   i. Serum creatinine ≤ 1.5 x ULN or Cr. Cl. ≥ 40ml/min/1.73m² (MDRD or CKD-EPI formula);

I8. Willingness and ability to comply with the study requirements;

I9. Signed and dated informed consent indicating that the patient has been informed of all the aspects of the trial prior to enrolment;

I10. Women of childbearing potential are required to have a negative serum pregnancy test within 72 hours prior to study treatment start. A positive urine test must be confirmed by a serum pregnancy test;

I11. Women of childbearing potential and male patients must agree to use adequate highly effective contraception for the duration of study participation and up to 5 months following completion of therapy;

I12. Patient must be covered by a medical insurance;

Non-inclusion criteria

E1. Prior malignancy within the last 3 years except for locally curable disease with no sign of relapse;

E2. Patients in whom imatinib had been already reintroduced after sunitinib as second line;

E3. Known D842V mutation in Exon 18 of PDGFRA;

E4. Previous treatment with immunotherapy;

E5. Any approved anticancer therapy (chemotherapy, hormonal therapy or radiotherapy) or treatment with any investigational product within 2 weeks prior to study treatments start;

E6. Residual adverse events from prior anticancer therapy that has not resolved to grade ≤1, except for alopecia and lab values (provided that inclusion criteria described in section 6.1 are met);

E7. Symptomatic metastases of Central nervous system requiring or having required steroids or enzyme-inducing anticonvulsants within 4 weeks before inclusion;

E8. Patients using or require to use while on the study of any prohibited concomitant and/or concurrent medications (see section "Prohibited concomitant/concurrent treatments) :

- Live, attenuated vaccines within 28 days prior to enrolment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed during the study active period,
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF-alpha agents) within 2 weeks prior to C1D1, or anticipation of need for systemic immunosuppressive medication during study treatment; with the exceptions of intranasal, inhaled, or topical corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or five half-lives of the drug (whichever is longer) prior to C1D1.
- Traditional herbal medicines since the ingredients of many herbal medicines are not fully studied and their use may result in unanticipated drug-drug interactions that may cause or confound assessment of toxicity,

E9. Patients with history of autoimmune disease including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barre syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix for a more comprehensive list of pre-existing autoimmune diseases and immune deficiencies) with the following exceptions:

- patients with a history of autoimmune-related hypothyroidism who are on thyroid replacement hormone,
- patients with controlled Type 1 diabetes mellitus,
- patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
  - rash must cover less than 10% of body surface area.

	- disease is well controlled at baseline and only requiring low potency topical steroids. - no acute exacerbations of underlying condition within the previous 12 months requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids **E10.** History of severe allergic or other hypersensitivity reactions to: ▪ chimeric or humanized antibodies or fusion proteins, ▪ biopharmaceuticals produced in Chinese hamster ovary cells, ▪ any active substance or to any of the chemical excipients of atezolizumab (refer to its IB) or imatinib (refer to its respective SmPC) **E11.** Patients with active infectious disease: ▪ severe infections within 4 weeks prior to randomisation including but not limited to hospitalization for complications of infection, bacteraemia, or severe pneumonia, ▪ active infection requiring antibiotics, ▪ active B or C hepatitis infection, *Note: Patients with past Hepatitis B Virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible. Patients positive for Hepatitis C Virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.* ▪ active tuberculosis ▪ HIV infection **E12.** Active or prior history of primary immunodeficiency; **E13.** Major surgical procedure within 28 days prior to study treatments start, or need for a major surgery during the course of the study; **E14.** Pregnant or breast-feeding women; **E15.** Patient that impairs their ability to swallow and retain imatinib or with impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of imatinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection) **E16.** Clinically significant unrelated systemic illness (e.g., significant cardiac, pulmonary, hepatic, or other organ dysfunction) that would compromise the patient's ability to tolerate study treatment or would likely interfere with study procedures or results. **E17.** Patients under tutorship or curatorship.
Study treatments	During the treatment period, all patients will receive either: • imatinib *per os* 400 mg daily continuously associated with intravenous admistrations of atezolizumab at the fixed dose of 1 200 mg every 3 weeks, • Or imatinib alone, *per os* 400 mg daily continuously. Study treatments will be administered for a maximum period of 12 months or until disease progression, unacceptable toxicity or patient's willingness to stop, whichever occurs first. Patient treated by imatinib and atezolizumab who experienced disease progression (iUPD according to iRECIST), may continue on treatment until disease progression confirmation

	(iCPD according to iRECIST) if he/she is clinically stable and still show clinical benefit. Patient who still experienced clinical benefit after 12 months can continue imatinib alone. Then, all patients will have surveillance until progression or until the end of the study.
Sample size	Assuming a 6-month PFS (6M-PFS) rate of 10% in the standard arm (imatinib alone) and a 6M-PFS rate of 30% as a clinically significant target for patient treated with imatinib associated to immunotherapy. The study was calibrated to detect a hazard ratio of 0.523 under the proportional hazards assumption and assuming the efficacy hypotheses mentioned above. A total of 100 events in the study would have 90% power to show statistically significant PFS at a 5% 2-sided level. Considering an accrual period of 36 months and a maximum follow-up time of 48 months, a **total of 102 patients will be randomized (51 per arm)**.
Expected study timelines	First patient in: Q1 2020 Last patient in: Q1 2023 Last patient Last visit: Q1 2024 Blind review and database lock: Q3 2024 Statistical report: Q1 2025 Publication: Q2 2025