

## Avapritinib real-life observatory

### SYNOPSIS Oct 2020

ACRONYM	AVIATOR2020 (AVapritinib real life observATORY)
TITLE	French long term registry with longitudinal follow up of PDGFRA D842V-GIST patients treated with Avapritinib
TYPE OF PROJECT	Prospective registry involving: <ul style="list-style-type: none"> <li>- the use of existing clinico-pathological data,</li> <li>- the prospective collection of data (treatment by Avapritinib, drug related side effects, test of cognitive functions, follow-up, vital status, death).</li> </ul>
FUNDING	Blueprint Medicines
SPONSOR	Centre de Lutte Contre le Cancer Léon Bérard
MEDICAL COORDINATOR	Dr Mehdi BRAHMI, medical oncologist
COORDINATING TEAM	<p>Centre de Lutte Contre le Cancer Léon Bérard</p> <p><u>Direction of translational research and innovation</u></p> <p><b>Project management team</b></p> <ul style="list-style-type: none"> <li>• Dr Françoise DUCIMETIÈRE, team manager</li> <li>• Dr Julien BOLLARD, project manager - <a href="mailto:julien.bollard@lyon.unicancer.fr">julien.bollard@lyon.unicancer.fr</a></li> <li>• Alexandra BIETTE, clinical research associate - <a href="mailto:alexandra.biette@lyon.unicancer.fr">alexandra.biette@lyon.unicancer.fr</a></li> </ul> <p><b>Department of Social and Human Sciences</b></p> <ul style="list-style-type: none"> <li>• Pr Véronique CHRISTOPHE, Health Psychology</li> </ul> <p><b>Data management</b></p> <ul style="list-style-type: none"> <li>• Claire CHEMIN-AIRIAU, clinical research associate</li> </ul> <p><b>Statistical team</b></p> <ul style="list-style-type: none"> <li>• Amélie ANOTA, Research Engineer/Statistician</li> </ul> <p><u>Direction of clinical research and innovation</u></p> <p><b>Legal &amp; Regulatory affairs</b></p> <ul style="list-style-type: none"> <li>• Julie STRUYF, Lawyer</li> <li>• Séverine GUILLEMAUT, Regulatory officer</li> </ul> <p><b>Department of Medical oncology</b></p> <ul style="list-style-type: none"> <li>• Dr Chiara RUSSO, Oncogeriatrics</li> <li>• Emilie PRETET-FLAMAND, Nurse in Oncogeriatrics</li> </ul>
SITES	≈11 sites inside/outside the sarcoma reference network (NETSARC+)
NUMBER OF PATIENTS	Approx. 45 patients

## RATIONALE

Gastrointestinal stromal tumors (GIST) are serious pathologies that are life-threatening. Worldwide, the annual incidence of GISTs is approximately 1.5 per 100,000 people, which represents about 800 to 900 new cases per year in France.<sup>1,2</sup> The Sarcoma Reference Network (NETSARC+), responsible for double reading and sarcoma multidisciplinary tumor board, performed 868 double readings of GIST in 2017, 762 in 2018 and 689 in 2019. GISTs represent about 15% of sarcomas and less than 1% of all malignant digestive tumors. They can occur at any level of the digestive tract, from the esophagus to the rectum. The most frequent locations are the stomach (60-70%) and the small intestine (20-30%). The median age at diagnosis is around 50-60 years, but they can occur at any age in life. Pediatric GISTs are rare and represent a distinct subgroup.

GIST are rare mesenchymal tumors of the gastrointestinal tract characterized by somatic mutations in the gene encoding the KIT (85%) or the PDGFR $\alpha$  (8%) protein.<sup>3</sup> Treatment of localized forms relies on adequate surgery without tumor spillage and sometimes systemic treatment with imatinib according to risk of relapse defined by localization, tumor size and mitotic count, as well as mutational status.<sup>1,2,4</sup> More than 40% of cases may recur and metastasize. Advanced and relapsing forms are currently treated with oral tyrosine-kinase inhibitors (TKI) of KIT and PDGFR such as imatinib (standard treatment), sunitinib (2<sup>nd</sup> line) and regorafenib (3<sup>rd</sup> line).<sup>5-7</sup> Nevertheless, imatinib has little or no activity in patients harboring the D842V mutation in the exon 18 of PDGFR $\alpha$  (20% of gastric GIST, 6% of all GIST patients).<sup>8,9</sup>

Moreover, patients with KIT mutation develop secondary drug resistance and no effective therapy is approved for GIST after failure of imatinib, sunitinib and regorafenib.<sup>10</sup> Consequently, other therapeutic alternatives are needed.

Avapritinib selectively inhibits many oncogenic KIT and PDGFR $\alpha$  mutations in GISTs, including those associated with primary and secondary resistance to approved treatment. Results from the phase I single-arm NAVIGATOR study show that avapritinib has significant efficacy in GIST patients with PDGFR $\alpha$  D842V mutation as well as in fourth line or higher (4L+). The overall response rate observed in this study was 86% in the overall population of patients with PDGFR $\alpha$  exon 18 mutant GIST, and 22% when used as fourth-line or later. The high objective response rate (ORR) and the long response duration of GISTs with a D842V mutation to avapritinib underline high efficiency.<sup>11</sup> In addition, both the ORR and the duration of response in 4L+ GISTs exceed those of the second and third line treatments approved to date.

The randomized phase III trial VOYAGER is currently evaluating the safety and efficacy of avapritinib in third or fourth line. Preliminary results will be reported in the second quarter of 2020. Completion date is expected in April 2023.

Investigators determined that avapritinib was a tolerable drug for the study patient population, with the safety profile showing mostly grade 1 and 2 adverse events (AEs), with cognitive effects in 41% of patients. The most common grade 3 and 4 treatment-related adverse events were anemia (16.2 %), fatigue (6.4 %), cognitive effects (3.9%), and diarrhea (2.9%). Treatment with avapritinib was discontinued for 8.3% of patients, and 2% of those experienced cognitive effects.<sup>12</sup>

Avapritinib is indicated as monotherapy for the treatment of adult patients with inoperable or metastatic GISTs with a D842V mutation in the PDGFR $\alpha$  receptor. An EMA application for a Marketing Authorization was filed on July 1st, 2019.

	<p>In France, an authorization for temporary use (ATU) starting on September 21<sup>st</sup> 2020 has been granted by the National Agency for Safety of Medicines and Health Products (ANSM). It allows the early availability of avapritinib in France without the AMM. This cohort ATU will be accompanied by a protocol of therapeutic use and collection of information (PUT) that describes the frequency of patient visits.</p> <p>The objective of this real life registry is to perform a long-term longitudinal follow up of PDGFRA D842V-mutated GIST patients treated with avapritinib and to collect effectiveness and safety data. It will be implemented in parallel to the cohort ATU until June 2023.</p>
OBJECTIVES	<p><b>Primary objective</b></p> <ul style="list-style-type: none"> <li>- Describe the survival of patient treated by Avapritinib in real life according to overall survival.</li> </ul> <p><b>Secondary objectives</b></p> <ul style="list-style-type: none"> <li>- To further assess the effect of Avapritinib according to: <ul style="list-style-type: none"> <li>o Progression Free Survival (PFS) after 12, 24 and 36 months</li> <li>o Incidence of long-term responders (&gt; 24 months)</li> <li>o Duration of treatment</li> </ul> </li> <li>- To assess the safety of Avapritinib <ul style="list-style-type: none"> <li>o Nature, frequency and severity AEs graded using Common Terminology Criteria for Adverse Events (CTCAE) V4.03</li> <li>o Evaluation of cognitive impairment in real-life according to FACT-Cog and Montreal Cognitive Assessment (MoCA) questionnaires</li> <li>o Evaluation of quality of life in real-life according to FACT-G questionnaire</li> </ul> </li> </ul>
PATIENT SELECTION	<p><b>Inclusion criteria:</b></p> <ol style="list-style-type: none"> <li>11. Adult (<math>\geq 18</math> years old), male or female</li> <li>12. Patient with a histologically or cytologically-confirmed diagnosis of unresectable or metastatic GIST harboring the D842V mutation in the PDGFR<math>\alpha</math> gene</li> <li>13. Patient treated by Avapritinib</li> <li>14. Non opposition to the use of her/his data</li> </ol>
GENERAL PLAN	<ol style="list-style-type: none"> <li><b>1. Routine identification of patient treated by Avapritinib and eligible to this study (prescribing physician and/or pharmacist)</b></li> <li><b>2. Inclusion of patient</b></li> <li><b>3. Collection of MoCa, FACT-Cog, FACT-G (each visit)</b></li> <li><b>4. Collection of retrospective and prospective data into the NETSARC+ database by a local CRA using the patient's Electronic Health Record</b></li> </ol>
EVALUATION OF COGNITIVE FUNCTION AND QUALITY OF LIFE	<p>As per the French Drug Administration's requirements (ANSM), the cognitive function will be assessed by the FACT-Cog and the MoCA questionnaires prior treatment start and every 3 months.</p> <p>The FACT-Cog questionnaire measures perceived cognitive deficits and related quality of life for adults undergoing cancer therapy. The MoCA questionnaire allows to screen for people with mild to severe neurocognitive impairment.<sup>13</sup></p> <p>Quality of life will be assessed using the FACT-G (Functional Assessment of Cancer Therapy-General) questionnaire. The latter is used to assess top-rated symptoms and concerns for a broad spectrum of advanced cancers in clinical practice and research.<sup>14</sup></p>

DURATION OF THE STUDY	Patient inclusion: 30 months, starting on November 2020. Patient follow up: 36 months
DATA COLLECTION	<p>An eCRF will be set up to collect all retrospective and prospective data:</p> <ul style="list-style-type: none"> <li>• Patient: Date of Birth, Sex, Date of last news, last news status, date of death, cause of death, previous cancer and prior family history of cancer.</li> <li>• Tumor: Date of initial diagnosis, PS (OMS), localization, date and presence of metastasis, presence of mutation.</li> <li>• Treatment: <ul style="list-style-type: none"> <li>○ Surgery (date, quality of resection, re-excision)</li> <li>○ External radiotherapy (localization, date, dose)</li> <li>○ Previous systemic treatment (line, classification code, name, date of beginning, date of end, reason for treatment interruption)</li> <li>○ Treatment by Avapritinib (line, date, posology, reason for stopping treatment, adverse event (code, date, grade, accountability to study treatments, treatment impact).</li> </ul> </li> <li>• Cognitive effect questionnaires: FACT-Cog &amp; MoCA (score at each question).</li> <li>• QoL questionnaire: FACT-G</li> </ul>
DATA QUALITY ASSURANCE	<p>Data entry will be performed online by clinician and authorized staff based on source documents. The sponsor is responsible for ensuring accuracy, completeness and timeliness of the data reported in the observatory.</p> <ul style="list-style-type: none"> <li>• <b>Data sources</b> <ul style="list-style-type: none"> <li>- Pathological and biological reports</li> <li>- Medical file</li> <li>- Multidisciplinary tumor board form</li> </ul> </li> <li>• <b>Data entry guide and collective data entry training</b></li> <li>• <b>Data checking procedure</b> <ul style="list-style-type: none"> <li>- Consistency checks for a number of parameters (an error message appears requesting to verify data entry, e.g.: Date, quantitative item...)</li> <li>- Data capture Help: items appear based on the response entered for the previous item</li> <li>- Check missing data percentage</li> </ul> </li> <li>• <b>Regular check of the investigational site</b> by a representative of the coordinating center to review project progress, data completeness and any emergent problems.</li> <li>• <b>On-site audits by a CRA</b> (all first patients of all participating centers (100%), then adaptation according to the filling quality of the center).</li> </ul>
STATISTICAL PLAN	See protocol.
ETHICAL AND REGULATORY ASPECTS	<p><b>Regulatory aspects</b></p> <p>This research involving the human person is classified as a category 3 non-interventional study) according to the French Jardé law (Ordinance No. 2016-800 of June 16<sup>th</sup>, 2016). The project will be authorized by the competent authorities and data privacy agency. The observatory will be compliant to General Data Protection Regulation (GDPR). Each Party is responsible for any personal data breach that falls into the sphere of such Party and shall comply with the obligations as set forth under Article 33 GDPR.</p> <p><b>Sites set-up</b></p>

	<p>All sites will be required to sign appropriate contracts with the Sponsor prior to participation. All participating investigators will be asked to sign the necessary agreements and supply a current CV.</p> <p>Sites will be provided with an investigator master file containing essential documentation, instructions, and other documentation required for the conduct of the registry.</p> <p><b>Patient information</b></p> <p>Patients will be informed of the purpose of the registry via an information letter. This form fully informs the patient of all aspects of the registry that are relevant to his decision to participate as required by local laws and regulations in force. Such information shall be clearly written and available to the patient.</p> <p>In case of consent withdrawal, the effective date of patient’s consent withdrawal should be noted on the source data and no data collection should be performed after that date. All data collected before that date will be analyzed.</p> <p><b>Access to data</b></p> <p>Access to the database and medical records will be granted to the sponsor, the treating physician and the CRAs in charge of the project.</p> <p>Data processing will be performed by authorized individuals including the sponsor, coordinating investigator, the data managers, the CRAs and the statisticians of CLB.</p> <p>All staff, bound by professional secrecy, must maintain the confidentiality of personal identity and personal medical information of patients. Data collection and analysis will comply with GDPR guidelines.</p>
<p>EXPECTED CONTRIBUTIONS FROM THE REGISTRY</p>	<p>This study will assess the effectiveness of Avapritinib in real-life in France and identify any serious and/or unexpected side effects due to its administration. This study will refine knowledge on Avapritinib and better assess its position in the therapeutic algorithm.</p>
<p>BIBLIOGRAPHY</p>	<ol style="list-style-type: none"> <li>1. Landi B, Blay JY, Bonvalot S, Brasseur M, Coindre JM, Emile JF, Hautefeuille V, Honore C, Lartigau E, Manton G, Pracht M, Le Cesne A, Ducreux M, Bouche O; Gastrointestinal stromal tumours (GISTs): French Intergroup Clinical Practice Guidelines for diagnosis, treatments and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO). <i>Dig Liver Dis.</i> 2019 Sep;51(9):1223-1231. doi: 10.1016/j.dld.2019.07.006. Epub 2019 Aug 3. Review.</li> <li>2. Casali PG, Abecassis N, Bauer S, Biagini R, Bielack S, Bonvalot S, Boukovinas I, Bovee JVMG, Brodowicz T, Broto JM, Buonadonna A, De Álava E, Dei Tos AP, Del Muro XG, Dileo P, Eriksson M, Fedenko A, Ferraresi V, Ferrari A, Ferrari S, Frezza AM, Gasperoni S, Gelderblom H, Gil T, Grignani G, Gronchi A, Haas RL, Hannu A, Hassan B, Hohenberger P, Issels R, Joensuu H, Jones RL, Judson I, Jutte P, Kaal S, Kasper B, Kopeckova K, Krákorová DA, Le Cesne A, Lugowska I, Merimsky O, Montemurro M, Pantaleo MA, Piana R, Picci P, Piperno-Neumann S, Pousa AL, Reichardt P, Robinson MH, Rutkowski P, Safwat AA, Schöffski P, Sleijfer S, Stacchiotti S, Sundby Hall K, Unk M, Van Coevorden F, Van der Graaf W, Whelan J, Wardelmann E, Zaikova O, Blay JY; ESMO Guidelines Committee and EURACAN. Gastrointestinal stromal tumours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. <a href="https://www.esmo.org/guidelines/sarcoma-and-gist/gastrointestinal-stromal-tumours">https://www.esmo.org/guidelines/sarcoma-and-gist/gastrointestinal-stromal-tumours</a>. <i>Ann Oncol.</i> 2018 Oct;29 Suppl 4:iv68-iv78.</li> <li>3. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. <i>Science.</i> 1998;279(5350):577-580.</li> <li>4. Debiec-Rychter M1, Sciot R, Le Cesne A, Schlemmer M, Hohenberger P, van Oosterom AT, Blay JY, Leyvraz S, Stul M, Casali PG, Zalcborg J, Verweij J, Van Glabbeke M, Hagemeyer A, Judson I; EORTC Soft Tissue and Bone Sarcoma Group; Italian Sarcoma Group; Australasian GastroIntestinal Trials Group. KIT mutations and dose selection for imatinib in patients with</li> </ol>

- advanced gastrointestinal stromal tumours. *Eur J Cancer*. 2006 May;42(8):1093-103. Epub 2006 Apr 18.
5. 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.
  6. Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, Heinrich MC, Tuveson DA, Singer S, Janicek M, Fletcher JA, Silverman SG, Silberman SL, Capdeville R, Kiese B, Peng B, Dimitrijevic S, Druker BJ, Corless C, Fletcher CD, Joensuu H. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med*. 2002 Aug 15;347(7):472-80.
  7. Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, McArthur G, Judson IR, Heinrich MC, Morgan JA, Desai J, Fletcher CD, George S, Bello CL, Huang X, Baum CM, Casali PG. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet*. 2006 Oct 14;368(9544):1329-38.
  8. Schvartsman G, Wagner M.J, Amini B, Zobniw C.M. Treatment patterns, efficacy and toxicity of regorafenib in gastrointestinal stromal tumour patients. *Sci. Rep*. 2017;7:9519.
  9. Cassier PA, Fumagalli E, Rutkowski P, Schöffski P, Van Glabbeke M, Debiec-Rychter M, et al. Outcome of patients with platelet-derived growth factor receptor alpha-mutated gastrointestinal stromal tumors in the tyrosine kinase inhibitor era. *Clin Cancer Res*. 2012;18:4458-64.
  10. Gajiwala KS, Wu JC, Christensen J, Deshmukh GD, Diehl W, DiNitto JP, English JM, Greig MJ, He YA, Jacques SL, Lunney EA, McTigue M, Molina D, Quenzer T, Wells PA, Yu X, Zhang Y, Zou A, Emmett MR, Marshall AG, Zhang HM, Demetri GD. KIT kinase mutants show unique mechanisms of drug resistance to imatinib and sunitinib in gastrointestinal stromal tumor patients. *Proc Natl Acad Sci U S A*. 2009 Feb 3;106(5):1542-7.
  11. AACR Project GENIE Consortium. AACR Project GENIE: powering precision medicine through an international consortium. *Cancer Discovery*. 2017;7(8):818-831.
  12. Heinrich MC, Jones RL, von Mehren M, et al, Clinical activity of avapritinib in  $\geq$  fourth-line (4L+) and PDGFRA Exon 18 gastrointestinal stromal tumors (GIST). Presented at: 2019 American Society of Oncology Annual Meeting; May 31- July 4, 2019; Chicago, Illinois. Abstract 11022.