Efficacy and Safety of PD-0332991 in Patients with Advanced Gastrointestinal Stromal Tumors Refractory to Imatinib and Sunitinib: A Phase 2 study

CYCLIGIST

Single-arm phase II study

Version n°4.0 du |15|03|2017| – N° IB: |2013|–|01|

Intégrant la modification substantielle N°1 du 06.06.2015
Intégrant la modification substantielle N°2 du 05.11.2015
Intégrant la modification substantielle N°3 du 11.03.2016
Intégrant la modification substantielle N°4 du 15.03.2017

EudraCT n° 2013-000283-28

Cet essai est soutenu par l'Institut National du Cancer et la Fondation ARC pour la Recherche sur le Cancer.

Coordinating Investigator
Antoine ITALIANO, MD, PhD
Medical Oncologist
Department of Medical Oncology
Institut Bergonié
229, cours de l'Argonne – 33076 BORDEAUX Cedex, France
Tel: 05.56.33.33.33 – Fax: 05.56.33.04.85 – E-mail: a.italiano@bordeaux.unicancer.fr

Clinical Research Unit
Simone MATHOULIN-PÉLISSIER, MD, PhD Institut Bergonié, Bordeaux
Head of the unit

Carine BELLERA, PhD Institut Bergonié, Bordeaux
Biostatisticien

David JUZANX Institut Bergonié, Bordeaux
Clinical Research Assistant

Barbara LORTAL
Emilie TOULZA Institut Bergonié, Bordeaux
Pharmacists

Pharmacovigilance
R&D Unicancer, Paris

SPONSOR **INSTITUT BERGONIÉ**

TABLE OF CONTENTS

APPROVAL AND SIGNATURES OF PROTOCOL

Study Title: **Efficacy and Safety of PD-0332991 in Patients with Advanced Gastrointestinal Stromal Tumors Refractory to Imatinib and Sunitinib: A Phase 2 study**

Competent Authority	Name : ANSM	Référence :	Autorisation initiale	13/11/2013
		131145A-12	Autorisation MSA1	18/09/2015
			Autorisation MSA2	07/03/2016
			Autorisation MSA3	12/05/2016
Ethic Comittee	Name : CPP du Sud-Ouest et d'Outre-Mer III	Référence :	Autorisation initiale	30/10/2013
		2013/81	Autorisation MSA1	26/08/2015
			Autorisation MSA2	16/12/2015
			Autorisation MSA3	27/04/2016
			Autorisation MSI4	26/04/2017

Noms et Titres des Responsables	Coordonnées	Date	Signature
Managing Director	**Pr François-Xavier MAHON** **Institut Bergonié – Bordeaux** **Tél:05.56.33.33.33 / Fax: 05.56.33.33.30** **Mail : e.bussieres@bordeaux.unicancer.fr**	15/03/2017	
Coordinating Investigator	**Dr Antoine ITALIANO** Institut Bergonie – Bordeaux Tel 05.56.33.78.05 / Fax : 05.56.33.04.85 Mail : a.italiano@bordeaux.unicancer.fr	15/03/2017	
Clinical Research Manager	**Pr Simone MATHOULIN-PELISSIER** Institut Bergonié – Bordeaux Tél : 05.56.33.33.98 / Fax: 05.56.33.04.66 Mail : s.mathoulin@bordeaux.unicancer.fr	15/03/2017	
Biostatistician	**Carine BELLERA** Institut Bergonie – Bordeaux Tel:05.56.33.04.95/Fax:05.56.33.04.85 Mail : c.bellera@bordeaux.unicancer.fr	15/03/2017	
Clinical Research Assistant	**David Juzanx** Institut Bergonié – Bordeaux Tél : 05.24.07.19.25 / Fax : 05.56.33.04.85 Mail : d.juzanx@bordeaux.unicancer.fr	15/03/2017	

I acknowledge having read the whole protocol, and I pledge to lead this protocol in accordance with the Good Clinical Practice, the Public Health Law No. 2006-806 of August 09, 2004 and the implementing Decree n° 2006-477 of April 26, 2006 and as described in this document.
I assume my responsibilities as referent investigator including:
- Collection of informed consent, dated and signed by patients before any selection procedure in the protocol,
- Validation of case report forms, completed for each patient included in the study,
- Direct access to source documents for verification by the clinical research assistant (CRA) commissioned by the sponsor,
- Archiving of critical documents of the study for a 15 year-period.

Name and address of the hospital:

Name of the Coordinating Investigator:

DATE : |__|__| |__|__| |__|__|__|__|

SIGNATURE :

LIST OF INVESTIGATORS

CENTRE 01 - Bordeaux
Institut Bergonié
Centre Régional de Lutte Contre le Cancer de Bordeaux et du Sud-Ouest
Département d'Oncologie Médicale
229, cours de l'Argonne
CS 61283
33076 Bordeaux Cedex
Tél : 05.56.33.32.44– Fax : 05.56.33.04.85

Dr. Antoine Italiano	**Mail : A.Italiano@bordeaux.unicancer.fr**
Dr Maud Toulmonde	Mail : m.toulmonde@bordeaux.unicancer.fr
Dr Sophie Cousin	Mail : s.cousin@bordeaux.unicancer.fr

CENTRE 02 – Dijon

Centre Georges-François LECLERC
Centre Régional de Lutte Contre le Cancer
Département d'oncologie médicale
1, rue Professeur Marioin – BP 77980
21079 DIJON cedex
Tel : 03.80.73.75.28 – Fax : 03.80.73.77.74

Docteur Nicolas Isambert	**Mail : nisambert@dijon.cgfl.fr**
Docteur Sylvie Zanetta	Mail : szanetta@dijon.cgfl.fr
Docteur Alice Hervieu	Mail : ahervieu@cgfl.fr

CENTRE 03 - Lille

Centre Oscar Lambret - Centre Régional de Lutte Contre le Cancer
Département d'oncologie générale
3 rue Frédéric Combemale
BP 307 – 59020 LILLE Cedex
Tél : 03.20.29.59.35 - Fax : 03.20.29.59.71

Docteur Nicolas Penel	**Mail : n-penel@o-lambret.fr**
Docteur Farid El Hajbi	Mail : f-elhajbi@o-lambret.fr
Docteur Yaovi(Eric) Amela	Mail : e-amela@o-lambret.fr
Docteur Frédrik Laestadius	Mail : f-laestadius@o-lambret.fr
Docteur Diane Pannier	Mail : d-pannier@o-lambret.fr

CENTRE 04 – Lyon

Centre Léon Bérard - Centre Régional de Lutte Contre le Cancer
Département d'oncologie médicale
28 rue Laënnec
69373 LYON Cedex 08
Tél : 04.78.78.27.57 – Fax : 04.78.78.28.51

Professeur Jean-Yves Blay	**Mail : jean-yves.blay@lyon.unicancer.fr**
Docteur Isabelle Ray-Coquart	Mail : isabelle.ray-coquard@lyon.unicancer.fr
Docteur Pierre Biron	Mail : pierre.biron@lyon.unicancer.fr
Docteur Philippe Cassier	Mail : philippe.cassier@lyon.unicancer.fr
Docteur Louis Tassy	Mail : louis.tassy@lyon.unicancer.fr
Docteur Olivia Bally	Mail: olivia.bally@lyon.unicancer.fr
Docteur Mehdi Brahmi	Mail: medhi.brahmi@lyon.unicancer.fr

CENTRE 05 – Marseille

Hôpital de la Timone - CHU
Département d'oncologie médicale
254 rue Saint Pierre
13385 MARSEILLE Cedex 05
Tél : 04.91.38.57.08 – Fax : 04.91.76.58.xx

Professeur Florence Duffaud	**Mail : florence.duffaud@mail.ap-hm.fr**
Docteur Sébastien Salas	Mail : sebastien.salas@ap-hm.fr

CENTRE 06– Nancy

Institut de Cancérologie de Lorraine – Alexis VAUTRIN
Service d'Oncologie Médicale
6 Avenue de Bourgogne - Cs 30519
54 519 VANDOEUVRE-LES-NANCY Cedex
Tél : 03.83.59.85.74 Fax : 03.83.59.83.59

Docteur Maria Rios	**Mail : m.rios@nancy.unicancer.fr**
Docteur Cyril Abdeddaim	Mail : c.abdeddaim@nancy.unicancer.fr

CENTRE 07 – Nantes

Institut de Cancérologie de l'Ouest - Site René Gaudducheau
Département d'oncologie médicale
Boulevard Jacques Monod
44805 NANTES SAINT HERBLAIN cedex
Tél : 02.40.67.99.39 – Fax : 02.40.67.97.76

Docteur Emmanuelle Bompas	**Mail : emmanuelle.bompas@ico.unicancer.fr**
Docteur Frédéric Rolland	Mail : frederic.rolland@ico.unicancer.fr
Docteur Damien Vansteene	Mail : damien.vansteene@ico.unicancer.fr
Docteur Carole Gourmelon	Mail : carole.gourmelon@ico.unicancer.fr
Docteur Akila Dandec	Mail : akila.dandec@ico.unicancer.fr
Docteur Marie Robert	Mail : marie.robert@ico.unicancer.fr

CENTRE 09 - Reims

CHU de Reims - Hôpital Robert Debré
Centre de Recherche et d'Investigation Clinique (CRIC) - Site HRD
unité 73 -7ième étage
Avenue du Général Koenig
51092 Reims Cedex
Tel : +33 (0) 3 26 78 78 14 - Fax : +33 (0) 3 26 78 92 19

Professeur Olivier Bouché	**Mail : obouche@chu-reims.fr**
Docteur Julien Volet	Mail : jvolet@chu-reims.fr

CENTRE 10 – Villejuif

Institut Gustave Roussy
Centre Régional de Lutte Contre le Cancer
Département d'oncologie médicale
39 rue Camille Desmoulins
94800 VILLEJUIF
Tél: 01.42.11.43.16 – Fax: 01.42.11.52.19

Docteur Axel Le Cesne	**Mail : axel.lecesne@gustaveroussy.fr**
Docteur Julien Domont	Mail : julien.domont@gustaveroussy.fr
Docteur Olivier Mir	Mail : olivier.mir@gustaveroussy.fr
Docteur Sarah Dumont	Mail : sarah.dumont@gustaveroussy.fr

SYNOPSIS

Title of the study	**Efficacy and Safety of PD-0332991 in Patients with Advanced Gastrointestinal Stromal Tumors Refractory to Imatinib and Sunitinib: A Phase 2 study**
Abbreviation of the trial	**CYCLIGIST**
Sponsor Identification	**Institut Bergonié** Centre Régional de Lutte Contre le Cancer de Bordeaux et du Sud-Ouest 229, cours de l'Argonne 33076 Bordeaux Cedex
Coordinating Investigator	**Docteur Antoine Italiano** **Department of Medical Oncology**
Number of investigational sites planned	9 Sites (France): - Institut Bergonié – Bordeaux - Centre Georges-François Leclerc – Dijon - Centre Oscar Lambret - Lille - Centre Léon Bérard – Lyon - Hôpital de la Timone – Marseille - Centre Alexis Vautrin – Nancy - Centre René Gauducheau – Nantes - Hôpital Robert Debré - Reims - Institut Gustave Roussy – Villejuif
Medical Conditions	Adult patients with Advanced Gastrointestinal Stromal Tumors Refractory to Imatinib and Sunitinib
Study Design	Exploratory, one-arm, multicenter, phase II clinical trial based on two-stage Simon's design
Number of Patients	63 patients will be recruited.
Duration of the study	• Beginning of inclusion: January 2014 • Inclusion period: January 2014 to June 2017 (42 months) • Length of patient participation: 18 months • Study length: 60 months
Objectives	**Main objective** To assess the antitumor activity of PD-0332991 in terms of non-progression at 16 weeks (after centralized review) in patients with documented disease progression while on therapy with imatinib and sunitinib for unresectable and/or metastatic GIST. **Secondary objectives** • To assess the antitumor activity of PD-0332991 in terms of : o Objective response rate (ORR) (as per RECIST v1.1 criteria) o Progression-free survival (PFS) (as per RECIST v1.1 criteria) o Non progression rate and ORR assessed using CHOI criteria o Overall survival • To assess correlation between ORR-RECIST and ORR-CHOI • To assess the safety of PD-0332991: Incidence of adverse events (AEs), serious adverse events (SAEs) and abnormal laboratory results (hematology, blood chemistry) will be assessed by the Common Terminology Criteria for Adverse Events (CTCAE), v4.0 • To assess the pharmacodynamic (PD) effect of PD-0332991 on gene expression profile in patient consenting to research biopsies (Optional study) before starting treatment and on treatment.
Inclusion Criteria	Patients eligible for inclusion in this study have to meet all of the following

	criteria: 1. Male or female patients ≥ 18 years of age 2. Histologically confirmed GIST of any anatomical location and confirmed by the RRePS Network ; positive immunohistochemical staining for c-KIT (CD117); or negative staining for KIT, but with either positive staining for DOG1 or an identified mutation of *KIT* or *PDGFRA* gene 3. Homozygous or heterozygous *CDKN2A* gene deletion assessed by array-comparative genomic hybridization (array-CGH) 4. Unresectable and/or metastatic disease with documented progression according to modified RECIST criteria (see section 7.2.1.5 of protocol) after 1st line imatinib and 2nd line sunitinib. Progression on the last line of treatment should be confirmed by central review with two radiological assessments identical (CT scans or MRI) obtained at less from 4 months interval within the 24 months before inclusion. 5. At least one measurable GIST lesion according to RECIST (v1.1 Appendix 3). A previously irradiated lesion is eligible to be considered as a measurable lesion provided that there is objective evidence of progression of the lesion prior to starting PD-0332991. 6. A performance status of 0, 1 or 2 according to the Eastern Cooperative Oncology Group (ECOG) scale(Appendix 1) 7. Recovery from Grade 2 to 4 toxicity related to prior line of treatment assessed according to NCICTCAE v.4.0 (Appendix 2) 8. Adequate bone marrow function as shown by: • Blood absolute neutrophil count (ANC) ≥ 1.5 x 109/L • Blood platelets ≥ 100 x 109/L • Blood hemoglobin (Hgb) > 9 g/dL 9. Adequate liver function as shown by: • Serum or plasma ALT and AST ≤ 3.0 x ULN (regardless of the presence or absence of metastases) • Serum or plasma total bilirubin: ≤ 1.5 x ULN (excepted for patients with Gilbert's syndrome) 10. Adequate renal function as shown by serum creatinine ≤ 2 x ULN 11. Patients who give a written informed consent obtained according to French and European regulations. 12. Patients affiliated to the French Social Security
Exclusion Criteria	1. Homozygous *RB1* gene deletion assessed by array-comparative genomic hybridization (array-CGH) 2. Patients who received anti-cancer drugs ≤ 5 days prior to starting PD-0332991 3. Patients who are treated or planned to be treated concomitantly with other cytotoxic or antineoplastic treatments, such as chemotherapy, immunotherapy, biological response modifiers, or radiotherapy 4. Patients with another primary malignancy within 2 years prior to starting the study drug, with the exception of adequately treated in-situ carcinoma of the uterine cervix, or completely excised (R0 resection) basal or squamous cell carcinoma of the skin 5. Patients with a corrected QT interval using Bazett's formula (QTcB) > 470 msec. 6. Current use or anticipated need for food or drugs that are known strong cytochrome P450 (CYP)3A4 inhibitors (i.e. grapefruit juice, verapamil, ketoconazole, miconazole, itraconazole, posaconazole, erythromycin, clarithromycin, tilithromycin, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir, nefazodone, diltiazem, and delaviridine) 7. Patients with impairment of gastrointestinal (GI) function or GI

	disease that may significantly alter the absorption of PD-0332991 (e.g. severe ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or extensive (>1m) small bowel resection, inability to swallow oral medications). Prior partial gastrectomy is not an exclusion criterion. 8. Patients with prior complete gastrectomy 9. Any of the following in the previous 6 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism. 10. Patients with any clinically significant medical or surgical condition which, according to investigators' discretion, should preclude participation - i.e. active or uncontrolled infection, uncontrolled diabetes, active or chronic liver disease (cirrhosis, chronic active hepatitis or chronic persistent hepatitis) - hepatitis B or C virus carriers with normal liver function tests, can be included 11. Known diagnosis of human immunodeficiency virus (HIV) infection. HIV testing is not mandatory 12. Patients who are currently receiving anticoagulation treatment with therapeutic doses • of warfarin or equivalent anticoagulant (e.g. high dose aspirin or clopidogrel or other) • or have an INR >1.5. Treatment with acetylsalicyclic acid 100 mg daily or low molecular weight heparin (LMWH) is allowed 13. Pregnant or breast-feeding women 14. Women of child-bearing potential not employing two effective methods of birth control. Effective contraception must be used throughout the trial and 24 weeks after the end of PD-0332991 (e.g. condom with spermicidal jelly, foam suppository or film; diaphragm with spermicide; male condom and diaphragm with spermicide, oral, implantable, or injectable contraceptives). Women of child-bearing potential defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months (i.e. who has had menses any time in the preceding 12 consecutive months), must have a negative serum pregnancy test ≤ 21 days prior to starting study drug. 15. Fertile males not willing to use contraception as stated above 16. Patients unwilling or unable to comply with the protocol.
Study drug formulation	PD-0332991 is formulated as gelatin capsules of 125 mg, 100 mg 75mg and 25 mg respectively.
Route of administration	PD-0332991 will be administrated orally
Administered dose	PD-0332991 dosed on a flat scale of 125 mg. Patients should be instructed to administrate PD-0332991 with a sufficient amount of water at least 1 hour prior to a meal or at least 2 hours following a meal and to swallow the required number of capsules at approximately the same time on each day. If the patient forgets to take the study treatment as described, he/she should skip the dose for that day and resume taking the PD-0332991 on the next scheduled day. The investigator or designee must instruct the patient to take PD-0332991 exactly as prescribed. All study treatments prescribed and dispensed to the patient and all dose changes during the study must be recorded on the CRF. Patients must be advised to bring their unused PD-0332991 capsules to the investigational site at each visit.
Treatment	PD-0332991 will be administrated on a 21 days on / 7 days off dosing

<table>
<tr><td>schedule</td><td>schedule.
One cycle is considered to consist of 4 weeks of PD-0332991 administration.
Patients will be treated with PD-0332991 until progression of disease, unacceptable toxicity, death or discontinuation for any other reason.</td></tr>
<tr><td>Dose modification and dose delay</td><td>If the patient forgets to take the study treatment as described, he/she should skip the dose for that day and resume taking the PD-0332991 on the next scheduled day.
For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. The following guidelines need to be applied.
<table>
<tr><td colspan="4">Table 2 : Dose reduction*</td></tr>
<tr><td></td><td>Starting dose level - 0</td><td>Dose level - 1</td><td>Dose level - 2</td></tr>
<tr><td>PD-0332991</td><td>125 mg</td><td>100 mg</td><td>75 mg</td></tr>
<tr><td colspan="4">*Dose reduction should be based on the worst toxicity demonstrated at the last dose.
**Dose reduction below 75 mg is not allowed.</td></tr>
</table></td></tr>
<tr><td>Treatment interruption and treatment discontinuation</td><td>○ Interruption
If the administration of PD-0332991 must be interrupted because of an unacceptable toxicity, study drug dosing will be interrupted or modified according to rules described in Table 3 (section 6.3.2.2 of protocol). A patient who requires a dose interruption (regardless of the reason for the interruption) lasting > 28 days (counting from the first day when a dose was missed) must discontinue PD-0332991. All treatment interruption must be recorded on the CRF.
Patients whose treatment is interrupted due to an adverse event or abnormal laboratory value must be followed at least once a week for 28 days and subsequently at 28 day intervals, until resolution or stabilization of the event, whichever comes first.

○ Discontinuation
PD-0332991 will be discontinued for any of the following reasons:
• Disease progression
• Consent withdrawal
• Unacceptable adverse events
• Major violation of the protocol
• A dose interruption of > 28 days or a dose delay of > 28 days from the intended day of the next scheduled dose
• Intercurrent illness that prevent further administration of treatment
• Pregnancy
• Need for any other types of anticancer therapy
• General or specific changes in the patient’s condition which render the patient unacceptable for further treatment at the discretion of the investigator
• Lost to follow-up
• Death.
If PD-0332991 is permanently discontinued, the patient will be considered to have completed study treatment. All patients must have safety evaluations for 28 days after the last dose of PD-0332991.
Patients who discontinue PD-0332991 should be scheduled for an End of Treatment Visit, whenever possible, after discontinuing PD-0332991, at which time all of the assessments listed for the End of Treatment Visit will be performed. The date and reason for stopping the study treatment</td></tr>
</table>

	should be recorded on the CRF.
Efficacy evaluation	Tumor assessment and response will be assessed according to RECIST v1.1, with same type of exam in regard of baseline. All potential sites of tumor lesions (target and non-target lesions) will be assessed using MRI or CT Scan with IV contrast of the Thorax Abdomen and Pelvis using a 5mm slice thickness with a contiguous reconstruction algorithm (a PET scan is not acceptable for radiological evaluation). Evaluation will be assessed: - at baseline within 21 days before the first dose of PD-0332991 - at D(28) of Cycle 1, at D(28) of Cycle 2 then every 8 weeks until month six and then every 12 weeks until disease progression or starting other treatment. A time window of 7 days is allowed for the radiologist to give his/her statement. Clinical suspicion of disease progression at any time requires a physical examination and radiological confirmation to be performed promptly rather than waiting for the next scheduled radiological assessment. Response regarding the first endpoint will be assessed by central radiology review. Whenever the criteria of response are met (Complete Response (CR) or Partial Response (PR)), the appropriate imaging tests will be repeated at least four weeks later in order to confirm the response. The decision regarding patient management will remain with the local investigator. In addition to RECIST v1.1 evaluation, all subject data acquired using contrast-enhanced CT will be evaluated according to Choi criteria. Choi reading will be performed locally.
Safety evaluation	Safety will be monitored by assessing all adverse events, including serious adverse events, the regular monitoring of hematology, blood chemistry, cardiac assessments and regular monitoring of vital signs and physical condition. These assessments should be performed ± 3 days of the scheduled day of assessment except for adverse events that will be evaluated continuously through the study (Refer to Table 5 of protocol). Scheduling of safety assessments for PD-0332991 cannot be changed due to dose interruptions. Refer to Section 6.3 of protocol for permitted PD-0332991 adjustments as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 10.2 of protocol.
Biomarkers (optional)	Fresh tumor biopsies FFPE (Formalin-Fixed Paraffin-Embedded) at screening and at Day 21 of Cycle 1 are encouraged to be collected. Once collected, the samples may be profiled by IHC, and array gene expression analysis to identify the pharmacodynamics activity of PD-0332991 in GIST patients. As this is an active area of research, several biomarkers may be analyzed if justified by results of internal or external research activities. Each sample will be sent to sponsor. All samples will be stored before they are analyzed (see section 7.2.4 of protocol for additional details).
Outcome variables	**Primary endpoint** Efficacy is assessed based on 4-month non progression. Non progression is defined as complete or partial response (CR, PR) or stable disease (SD), using the Response Evaluation Criteria in Solid Tumors (RECIST

	v1.1). Non-progression rate will be calculated as the number of alive and progression free patients divided by the number of eligible and assessable patients for the efficacy analysis. Eligible and assessable populations are described in corresponding section of protocol. As recommended by RECIST v1.1, all claimed response will be centrally reviewed by an expert of the study. The results of the centralized radiological review will be used for the analysis of the primary endpoint. **Secondary endpoints** • Objective response is defined as complete response (CR) or partial response (PR) according to RECIST v1.1. • Progression-free survival is defined as the time from the first administration of treatment to progression (as per RECIST v1.1) or death of any cause, whichever occurs first • Overall survival is defined as the time from the first administration of treatment to death. • Progression will also be assessed using CHOI criteria • Safety of PD-0332991 will be assessed by the Common Terminology Criteria for Adverse Events (CTCAE), v4.0
Statistical considerations	**Sample size calculation** The primary evaluation endpoint is the non-progression rate at 4 months. - We rely on an optimal two-stage Simon's design (Simon, 1989). Based on the following hypotheses under PD-0332991 treatment: • 25% non-progression rate (null hypothesis), • 45% acceptable non-progression rate (alternative hypothesis), • 5% type I error rate, • 90% power, A total of 57 assessable subjects will be necessary, with 22 assessable subjects recruited to the first stage. - Stage 1: Following the inclusion of the first 22 assessable patients, if 6 or less patients are progression-free (complete response, partial response or stable disease), the study will be terminated early. Otherwise, the second group of 35 subjects will be recruited. - Stage 2: If at the end of recruitment, 20 patients or more are progression-free (out of the 57 evaluable patients), PD-0332991 will be considered worthy of further testing in this disease. Eligible and assessable populations are described in corresponding section of protocol. Given the disease is rare and the absence of standard treatment in this indication, inclusion will not be suspended after the recruitment of the first 22 patients. Inclusion will be pursued, while data on the first 22 patients will be analyzed. In order to account for not evaluable patients (+/- 10%), 63 patients will be recruited. The anticipated accrual rate is 3-4 patients/months.
Duration of Study period (per patient)	Patients will be evaluated at scheduled visits in up to three study periods: • Pre-treatment (PRE TT): from signature of informed consent to the first treatment by PD-0332991. • Treatment (TT): from the first treatment by PD-0332991 to the first 28 days following the last PD-0332991 administration. • Follow-up (FUP): after treatment discontinuation, all patients must be followed up for 28 days after the last dose of the study drug for safety assessment (AEs and/or SAEs). Patients will be considered to be on-study from the signature of the

	informed consent to the end of follow-up period. All patients will be followed up every 3 months for survival for one year and information will be documented in the source documents and in CRF. Patients will be followed for progression. Any patient who is discontinued from PD-0332991 for any reason (except for death, disease progression, lost to follow-up, subject/guardian decision [withdrawal of consent], or study termination) will continue to have tumor assessments performed every 3 months until radiological progression, start of new anticancer therapy or death

Schedule of assessments and procedures

	Pre-Screening phase	Screening/Baseline	Cycle 1		Cycle N	End of Study Treatment	Survival Follow-Up
Visit Name			V1	V2	Vn		
Day of cycle		-21 to -1	Day 1	Day 15	Day 1	Within 28 days after discontinuation of study drug	
Obtain Informed Consent	X						
CDKN2A gene deletion assessed by array-CGH (centralized to Bergonie Institute)	X						
Patient history							
Demography		X					
Inclusion/exclusion criteria		X					
Relevant medical history/current medical conditions		X					
Diagnosis and extent of cancer		X					
Prior antineoplastic therapy		X					
Prior/concomitant medications		X	Continuous until 28 days post-late dose of study drug				
Antineoplastic therapies since discontinuation of study treatment							X
Clinical exam							
Physical examination		X	X	X	X	X	
Performance status		X	X	X	X	X	
Height/Weight		X	X	X	X	X	
Vital signs		X	X	X	X	X	
Laboratory assessments							
Hematology		X	X	X	X Days 1 and 15	X	
Chemistry		X	X	X	X	X	
Coagulation		X	X	X	X	X	
Pregnancy test		X	X		X	X	
Imaging/Other assessments							
Tumor evaluation: CT scan or MRI		Day-21 to -1	D(28) of Cycle 1, D(28) of Cycle 2 then every 8 weeks until month six and then every 12 weeks				
ECG		X	X	X	X	X	
Safety							

Adverse events			Continuous until 28 days post-late dose of study drug				
Biomarkers (Optional study)							
Tumor biopsy Day –3 to Day -1 Day 21 cycle 1		X	Day 21 Cycle 1				
Others							
PD-0332991 administration			21-days on, 7 days off				
Reason for withdrawal						X	
Survival update every 3 months for one year							X

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE(s)	Adverse Event(s)
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Air Under Curb
βhCGs	Beta Human Chorionic Gonadotrophins
BCRP	Breast Cancer Resistant Protein
BSC	Best Supportive Care
BUN	Blood Urea Nitrogen
CDK	Cyclin-dependent Protein Kinase
CGH	Comparative Genomic Hybridization
CPK	Creatine Phosphokinase
CR	Complete Response
CRP	C-Reactive Protein
CRF	Case Report Form
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of Variation
DLT	Dose-limiting Toxicity
DNA	Deoxyribonucleic Acid
DR	Duration of Response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EMEA	European MEdecin Agency
EPO	Transfusion and/or Erythropoietin
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
FUP	Follow-up
GCP	Good Clinical Practice
GGT	Gamma-Glutamyltransferase
GI	Gastro Intestinal
GIST	Gastrointestinal Stromal Tumors
HCG	Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HPLC	High-performance Liquid Chromatography
HR	Heart Rate
IB	Investigator's Brochure
IC50	Half-maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Investigational Ethics Committee
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
LPLV	Last Patient Last Visit
LD	Longest Diameter
LDH	Lactate Dehydrogenase
LMWH	Low Molecular Weight Heparin
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall Response Rate

OS	Overall Survival
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PFS	Progression-free Survival
P-gp	P-glycoprotein
PR	Partial Response
PRE TT	Pre-treatment
PS	Performance Status
PT	Prothrombin Time
QD	Quotidien Dose
RBC	Red Blood Cell
RD	Recommended Dose
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RP2D	Recommend Phase 2 Dose
RT	Plasma-to-blood Ratio
SAE(s)	Serious Adverse Event(s)
SCID	Severe Combined Immunodeficiency
SD	Stable Disease
STS	Soft Tissue Sarcoma
TKI	Tyrosine Kinase Inhibitor
TT	Treatment
TTP	Time to tumor Progression
ULN	Upper Limit of Normality
US	United State
USPI	U.S. Package Inserts
VEGF	Vascular Endothelial Growth Factor
VGPR	Very Good Partial Response
WBC	White Blood Cells
WHO	World Health Organization

1. Background

1.1 Overview of disease pathogenesis, epidemiology and current treatments

Mesenchymal tumors of the gastrointestinal tract, most of which originally classified as leiomyoma or leiomyosarcoma, have been termed stromal tumors (Mazur and Clark 1983), (Hamilton and Aaltonen 2000), (Corless et al 2004). More recently, it has become clear that gastrointestinal stromal tumors (GIST) are the most frequent mesenchymal tumors of the gastrointestinal tract. GIST are thought to arise from the interstitial cells of Cajal (Perez-Atayde et al 1993) which compose the myenteric plexus found in the stomach and bowel. These tumors are most frequently located in the stomach (50–60%), small bowel (20–30%), and large bowel (10%), with the esophagus, mesentery, omentum, and retroperitoneum accounting for the remaining cases (Fletcher et al 2002). On the basis of population-based incidence rates in Sweden (Nilsson et al 2005), it has been estimated that approximately 5000 new cases of GIST are diagnosed each year in the US with similar incidence rates being reported in the EU (Corless et al 2004). GIST occur predominantly in middle-aged and older people, with a median age of approximately 60 years and no apparent gender preference (Hamilton and Aaltonen 2000, De Giorgi and Verweij 2005).

GIST may display a variety of phenotypic features, many of which correlate with patient prognosis. Thus, there is an emphasis on tumor size and mitotic index for risk stratification of primary GIST, with such risk being correlated with tumor recurrence (Fletcher et al 2002). At the present time, risk stratification based on pathologic criteria is preferable to the use of such terms as benign or malignant GIST (Corless et al 2004). Patients with a gastric GIST seem to fare slightly better than those with intestinal primary tumors (Emory et al 1999). GIST have a tendency to recur both locally and in the form of peritoneal and liver metastases, with lymphnode metastases being infrequent (Corless et al 2004). Surgical resection is the mainstay of therapy for primary GIST, a disease that is typically refractory to cytotoxic chemotherapy (DeMatteo et al 2000, Plaat et al 2000).

The diagnosis of GIST has been facilitated by the discovery that these tumors stain positively with an immunohistochemical marker (CD117) previously used to stain the interstitial cells of Cajal (Hirota et al 1998, Kindbolm et al 1998). The antibody used in the immunohistochemical reaction recognizes KIT, a membrane receptor for stem-cell factor (Yarden et al 1987). Currently, KIT expression is a major diagnostic criterion for GIST, and few other KIT-positive mesenchymal tumors of the gastrointestinal tract are likely to be confused with GIST; notable exceptions include metastatic melanoma and malignant vascular tumors (Miettinen et al 2002). Approximately 95% of GIST stain positively for CD117 (Corless et al 2004). In most of these cases, somatic mutations can be found in the gene encoding the KIT protein, typically in exons 11 and 9 (more rarely in exon 13 or exon 17) (Hirota et al 1998, Corless et al 2004). These mutations confer a gain of function to the receptor, which becomes constitutively activated regardless of the presence of its ligand, stem-cell factor. In some cases of GIST, no mutation is found in KIT. The search for additional molecular abnormalities led to the discovery that in many KIT-negative GIST there is a somatic mutation in the gene encoding the platelet-derived growth-factor receptor (PDGFR) (Heinrich et al 2003, Hirota et al 2003). PDGFR is closely related to KIT, and also belongs to the type III family of receptor tyrosine kinases (Rousset et al 1995). Mutated KIT or PDGFR confer a growth advantage to tumor cells, and have recently become targets for therapeutic intervention.

Imatinib is an oral tyrosine-kinase inhibitor that has revolutionized the treatment of GIST, since this drug is able to inhibit the tyrosine-kinase activities of KIT and PDGFR Buchdunger et al 1996, Heinrich et al 2003, Joensuu et al 2001). Imatinib was approved in February 2002 for the treatment of patients with metastatic and/or unresectable GIST, and the recommended dose was 400 or 600 mg daily (Dagher et al 2002). The approval was based on a pivotal Phase II trial, in which 147 patients with metastatic and/or unresectable GIST were randomized to treatment with daily doses of imatinib of 400 mg (N=73) or 600 mg (N=74).
The combined response rate by Southwest Oncology Group criteria in the two arms of the study was 53.7% (Demetri et al 2002). More recently, imatinib was approved for the treatment of patients with GIST, who have had surgery to remove their cancer and are at significant risk of the cancer returning. Data supporting this new use for Glivec demonstrates that 98% of patients receiving 400mg Glivec daily for a year after surgery to remove their GIST did not experience their tumors returning after 12 months compared to 83% of patients taking placebo.
Some patients do not derive benefit from conventional-dose imatinib, while others develop resistance after several months of successful treatment. For all such patients, current therapeutic options are limited. Conventional modalities such as chemotherapy and radiation therapy have proven to have limited efficacy for the treatment of patients with GIST. Among patients with unresectable or metastatic disease at diagnosis, the ESMO guidelines recommend treatment with imatinib until disease progression (ESMO Guidelines, 2010).
When there is disease progression, the ESMO guidelines recommend continuing tyrosine kinase inhibition with increased daily doses of imatinib (800 mg) or with sunitinib. However, resistance to imatinib may develop and represents a clinical challenge. Sunitinib has been approved in 2009 by the European Commission for patients whose disease has progressed or who are intolerant to imatinib therapy. A Phase III study of sunitinib versus placebo in patients who had progressed during imatinib therapy was terminated early because of positive interim results. Time to tumor progression (TTP) was 6.3 months on sunitinib versus 1.5 on placebo and sunitinib reduced the risk of death by approximately 50% compared to placebo (Demetri et al 2006).

1.2 Introduction to investigational treatment(s) and study rationale

1.2.1 Overview of PD-0332991

PD-0332991 is a highly selective inhibitor of CDK4/CYCLIND1 kinase activity (IC50: 11 nM, K_i= 2nM) with little or no activity against a large panel of 34 other protein kinases including other CDKs and a wide variety of tyrosine and/serine threonine kinases. Cdk6, another enzyme that also complexes with cyclin-D subunits, is also commonly expressed in mammalian cells and tumors. Cdk6 is highly homologous to Cdk4 and can perform the same function by phosphorylating Rb, thus potentially creating a redundant mechanism to promote cell cycle progression.
Consequently, inhibition of both enzymes is necessary to ensure complete suppression of Rb phosphorylation and the greatest possible spectrum of antitumor activity. Results indicate that PD-0332991 inhibits Cdk6 with equivalent potency to Cdk4.
PD-0332991 inhibits tumor growth of several types of human xenograft tumors (SF-295, MDA-MB-435, Colo-205, and others), grown in SCID mice. Estimated steady-state plasma concentrations of 1000 ng/mL resulted in 80% to 90% inhibition of

phospho-Rb formation and 50% reduction of tumor growth. Reduction in phospho-Rb was rapidly reversible as plasma PD-0332991 concentrations declined.
In nonclinical species (rat, dog, and monkey), PD-0332991 exhibits low to moderate plasma clearance, large volume of distribution, and moderate oral bioavailability ranging from 23% to 56%. Plasma protein binding of PD-0332991 is moderate in mouse, rat, dog, and human plasma. PD-0332991 shows a preferential distribution to red blood cells over plasma in humans, but similar distribution between red blood cells and plasma in nonclinical species.
Radioequivalents were widely distributed to most rat tissues and fluids following an oral dose of [$_{14}$C]PD-0332991, with radioactivity levels consistently greater than those observed in blood. PD-0332991 is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog, and human liver microsomes. In vitro, PD-0332991 is primarily metabolized by CYP3A enzymes. Following oral administration of [$_{14}$C]PD-0332991 to intact and bile duct-cannulated rats, the metabolic pathways involve oxidation, glucuronidation, sulfation, and combinations of these reactions. Identified oxidative metabolites were qualitatively similar between in vitro and in vivo studies. In rats, [$_{14}$C]PD-0332991 was mainly eliminated via the feces (>82% within 168 hours); the high fecal elimination occurred via biliary excretion (53% to 82% within 72 hours recovery in bile). PD-0332991 and its oxidative metabolite, PF-05089326, demonstrated little or no inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 enzyme activities and thus, showed low potential for CYP-mediated pharmacokinetic drug interactions. However, PD-0332991 and PF-05089326 caused time-dependent inhibition of CYP3A midazolam 1'-hydroxylase and testosterone 6β-hydroxylase activities with K_i and k_{inact} values for PD-0332991 of 10 μM, 0.036 min^{-1} and 19 μM, 0.087 min^{-1} and for PF-05089326 of 7.0 μM, 0.094 min^{-1} and 6.4 μM, 0.15 min^{-1}, respectively. Therefore, PD-0332991 and its metabolite may have the potential for pharmacokinetic drug interactions with compounds for which CYP3A-mediated metabolism constitutes the primary mechanism of clearance.
The potential interaction of PD-0332991 with efflux transporters P-glycoprotein (P-gp) and breast cancer resistant protein (BCRP) was investigated in vitro using digoxin and talinolol substrates. The percent inhibition of digoxin and talinolol efflux reached 42% and 71% for P-gp and 44% and 74% for BCRP at the highest measured PD-0332991 concentration (6.09 μM). Therefore, PD-0332991 may have the potential to affect the absorption and/or pharmacokinetics of drugs that are substrates of P-gp or BCRP.
PD-0332991 had no effect on heart rate, rhythm, or blood pressure in dogs given single oral doses of 10 and 30 mg/kg (200 and 600 mg/m$_2$, respectively); however, evidence of QT prolongation was noted at both doses. Corresponding C_{max} and $AUC_{(0-24)}$ values associated with these doses were □511 ng/mL and □8800 ng•h/mL, respectively. PD-0332991 inhibited hERG current in HEK293 cells and increased action potential duration at 90% repolarization in Purkinje fibers consistent with QT prolongation observed in vivo.
Significant and transient pulmonary effects occurred in anesthetized dogs given a single IV dose of PD-0332991 at 5 mg/kg (100 mg/m$_2$). Associated observed peak plasma drug concentrations were □2040 ng/mL. These effects were consistent with centrally mediated respiratory depression. No changes in pulmonary function were noted in dogs with observed peak plasma concentrations □414 ng/mL at 1 mg/kg (20 mg/m$_2$).
In pivotal repeated-dose toxicology studies, PD-0332991 was lethal in rats; associated steady-state $AUC_{(0-24)}$ values were 46,600 and 11,100 ng•h/mL in males and females, respectively. The reason for increased susceptibility of females for

lethality on an exposure basis is unknown. Reversible bone marrow pancytopenia occurred in male and female rats at ≥50 mg/kg (300 mg/m2) and ≥100 mg/kg (600 mg/m2), respectively. Changes in males resulted in decreased peripheral blood cell counts. Testicular degeneration occurred in rats at ≥50 mg/kg and was progressive in severity throughout the reversal period (1-month treatment-free observation period). Rales and tracheal mucosal atrophy occurred in male rats at ≥50 mg/kg and in female rats at ≥100 mg/kg. Target organ toxicity in rats generally occurred to a greater extent in males than in females at equivalent doses and may have been related to systemic drug exposures that were significantly higher in males (17,300 to 46,600 ng•h/mL) than females (2530 to 11,100 ng•h/mL). Dose- and time-dependent decreases in hematology parameter values occurred in dogs given PD-0332991 at ≥0.6 mg/kg (12 mg/m2); associated steady-state $AUC_{(0-24)}$ values were ≥548 ng•h/mL. Neutrophils and monocytes were most affected; the nadir occurred at the end of dosing, and all changes were reversible. Reversible bone marrow pancytopenia and lymphoid depletion occurred in dogs at ≥0.6 mg/kg. Testicular degeneration occurred in dogs at ≥0.6 mg/kg and was progressive in severity throughout the reversal period.
PD-0332991 was not mutagenic in bacteria or clastogenic in human lymphocytes in vitro with or without metabolic activation. PD-0332991 was positive for micronucleus formation in vitro, and in male rats following oral administration. Additional work demonstrated that PD-0332991 may have aneugenic potential.
Based on results from in vitro testing in the 3T3 neutral red uptake assay, PD-0332991 is considered non-phototoxic.
As of 30 September 2011, 4 clinical studies with PD-0332991 are ongoing:
1. A Phase 1 dose-escalation single agent study in patients with advanced cancers or lymphomas (A5481001). Seventy-four patients have been dosed. Enrollment is closed.
2. A Phase 1 single-agent study in patients with relapsed/refractory mantle cell lymphoma (A5481002). Seventeen patients have been dosed. Enrollment is closed.
3. A Phase 1/2 study in combination with letrozole in patients with advanced breast cancer (A5481003). Sixty-four patients have been enrolled and treated in this study.
4. A Phase 1/2 study in combination with bortezomib and dexamethasone (A5481004) in patients with relapsed/refractory multiple myeloma. Fifty-one patients have been enrolled and treated in this study.
The Phase 1 dose-escalation study of PD-0332991 (A5481001) evaluated two different oral dosing schedules: Schedule 3/1 (3 weeks on treatment/1 week off treatment) and Schedule 2/1 (2 weeks on treatment/1 week off treatment). The recommended Phase 2 dose (RP2D) for Schedule 3/1 and Schedule 2/1 was determined to be 125 mg QD and 200 mg QD, respectively. Overall, the adverse events (AEs) reported in this study were manageable and reversible. The dose-limiting toxicities (DLTs) that occurred during this study were similar between the two dosing schedules and consisted of myelotoxic events, i.e. neutropenia, thrombocytopenia, and/or anemia. The myelosuppression was reversible, not cumulative, and non complicated, and resulted in treatment discontinuation in only one patient. While the safety profile of the two schedules was comparable, greater long-term antitumor activity was observed with Schedule 3/1, therefore such regimen was selected for further clinical development.
The safety profile observed thus far in the combination studies A5481003 and A5481004 appears consistent with that of PD-0332991 as a single agent and is mainly characterized by neutropenia, thrombocytopenia, and/or anemia. Nausea, diarrhea, constipation, and fatigue were also noted in PD-0332991 studies.

As far as antitumor activity is concerned, one patient with testicular cancer enrolled to study A5481001 achieved a confirmed partial response. In that same study, 32% of patients with a variety of tumor types experienced stable disease for two or more cycles of treatment, 24% for 4 or more cycles, and 13% for 10 or more cycles. A total of 5 patients experienced stable disease for 20 or more cycles.
In patients with refractory mantle cell lymphoma (Protocol A5481002), as of 30 September 2011, a total of 3 subjects achieved a best response of either PR (2 subjects [12.5%]) or CR (1 subject [6.3%]). The overall ORR of the 16 patients evaluable for response was 18.8% (95% CI: 4.0% to 45.6%). Seven subjects (43.8%) had a best response of SD/no response.
Both median time to progression (TTP) and progression-free survival (PFS) were 5.5 months (95% CI: 2.0 to 18.6 months). The probability of being event-free at Month 12 was 36.4% (95% CI: 11.1 to 61.6%). Due to the small number of subjects who had a response, duration of response (DR) was not calculated.
The response data from the Phase 1 portion of Study A5481003 showed that of the 9 patients with measurable disease (3 patients with bone only disease), 3 patients (33%) achieved a PR.
Another 5 patients (42%) had stable disease for □6 months, and the clinical benefit rate was 67% (PR + SD □6 months). Response data for the Phase 2 portion of this trial is not mature and will not be presented at the time of this summary.
The response data from the Phase 1 portion of Study A5481004 showed that 2 patients achieved a very good partial response (VGPR). In Phase 2, of the 30 patients treated, 25 patients were evaluable for response. Of the 25 patients, 1 patient achieved a complete response (CR), 1 patient VGPR, and 3 patients achieved PR.
Pharmacokinetic data from study A5481001 indicate that plasma pharmacokinetics of PD-0332991 are low to moderately variable with generally dose proportional exposures over the dose range evaluated. PD-0332991 is slowly absorbed with a half-life of ~27 hours.
Renal excretion was determined to be a minor route of elimination. In the pilot food effect assessment, higher exposures and peak concentrations were observed in the fed state compared to the fasted state. Based on these data, it was concluded that since administration of PD-0332991 with a high fat meal may increase PD-0332991 exposure, patients should be fasted from 1 hour before to 2 hours after dosing, unless otherwise indicated in clinical protocols. The effects of a non-fat meal on the pharmacokinetics of PD-0332991 have not been evaluated.
Interpretation of these data and the possible risks associated with administration of PD-0332991 to humans are summarized in Section 7 of the ongoing Investigator's Brochure.

1.2.2 Study rationale and purpose

As mentioned in Section 1.1, the treatment of advanced GIST patients is based on imatinib followed with sunitinib in case of resistance/intolerance. However, the median progression-free survival (PFS) on sunitinib is frequently short, and after failure with both imatinib and sunitinib, treatment remains controversial. Patients who fail to respond or have progression after therapy with these two drugs have a grim prognosis. Given the limited options for the third-line treatment of patients with imatinib- and sunitinib-refractory/intolerant GIST, there is a need for novel therapeutic strategies.
The so-called molecular signature "CINSARC" is a strong and validated predictor of metastasis in patients with GISTs (Lagarde et al., 2012). Remarkably, none of the

patients assigned to the good prognosis group developed metastases or relapsed. The CINSARC signature comprises 67 genes involved in maintenance of chromosome integrity and mitotic control, indicating that these processes play a crucial role in the development of metastasis in sarcomas (Chibon et al., 2010). The top-ranked gene being overexpressed in this signature was *AURKA*. The AURKA protein is a mitotic centrosomal protein kinase amplified in many cancer types (Marumoto et al., 2005). *AURKA* overexpression induces centrosome duplication and segregation abnormalities leading to aneuploidy and malignant transformation (Marumoto et al., 2005). Whole chromosome losses are the most frequently observed alterations in GISTs and are assumed to originate from unequal chromosome segregation, which can be induced by AURKA overexpression (Schvartzman et al. 2010). Contrary to the mechanism seen in other cancers, we have shown that AURKA overexpression in GISTs is not explained by gene amplification, but is instead a secondary change we postulate to be caused by defects in Restriction point control. Indeed, *CDKN2A* deletion is frequently deleted in GIST with metastatic relapse (Lagarde et al. 2012). In the few cases of high-risk gist lacking *CDKN2A* deletion, the *RB1* gene is deleted. This suggests a strong association between *CDKN2A* deletion, *RB1* deletion, *AURKA* expression, CINSARC score, and metastasis in GIST.
CDKN2A is located at 9p21 chromosome and encodes 2 key tumor suppressor proteins, p16INK4a and the p14ARF, which regulate the Restriction point and p53, respectively. Previous studies on GISTs have linked 9p21 alterations to tumor progression (El-Rifai et al. 2000; Kim et al., 2000; Schneider-Stock et al., 2003; Schneider-Stock et al., 2005; Romeo et al. 2009; Haller et al., 2008) but the driver gene was not positively identified (*CDKN2A*, *CDKN2B*, or *MTAP*) (Astolfi et al., 2010; Belinsky et al., 2009; Perrone et al., 2005; Assamaki et al. 2007; Huang et al., 2009). A recent study has shown that homozygous 9p21 deletions target *CDKN2A* and more specifically p16INK4a 4. Most of the CINSARC genes are known to be under the transcriptional control of E2F. RB1 sequesters E2F, which is released from the complex upon RB1 phosphorylation by CDK4. CDK4 is, in turn, inhibited by p16INK4a. Hence, we hypothesize that alteration of the restriction point via deletion of p16INK4a (and more rarely of RB1: 20% of cases) gene in GISTs is likely to be a causative event that leads to the overexpression of CINSARC genes, which in turn induce chromosome instability and ultimately metastasis. Low p16INK4a expression was associated with response to PD-0332991 in several in vitro tumor models. (Konecny et al. 2011; Katsumi et al. 2011; Finn et al. 2009). Considering our molecular data, we believed that PD-0332991 warrants clinical investigation in advanced gastrointestinal stromal tumors with alteration of p16INK4a. This alteration is detectable by comparative genomic hybridization which is a technique highly manageable in the context of routine clinical care and clinical trial.

2. Objectives and endpoints

2.1 Main objective

To assess the antitumor activity of PD-0332991 in terms of non-progression at 16 weeks (after centralized review) in patients with documented disease progression while on therapy with imatinib and sunitinib for unresectable and/or metastatic GIST.

2.2 Secondary objectives

- To assess the antitumor activity of PD-0332991 in terms of :
    - Objective response rate (ORR) (as per RECIST v1.1 criteria Appendix 3)

  - Progression-free survival (PFS) (as per RECIST v1.1 criteria Appendix 3)
  - Non progression rate and ORR assessed using CHOI criteria (Appendix 4)
  - Overall survival
- To assess correlation between ORR-RECIST and ORR-CHOI
- To assess the safety of PD-0332991: Incidence of adverse events (AEs), serious adverse events (SAEs) and abnormal laboratory results (hematology, blood chemistry) will be assessed by the Common Terminology Criteria for Adverse Events (CTCAE), v4.0. (Appendix 4)
- To assess the pharmacodynamic (PD) effect of PD-0332991 on gene expression profile in patient consenting to research biopsies (Optional study) before starting treatment and on treatment.

3. Study design

This is a multicentre single-arm Phase II study evaluating the efficacy and safety of orally PD-0332991, 125 mg/day, 21 days on/7 days off, in patients with documented disease progression while on therapy with 2nd line sunitinib for unresectable and/or metastatic GIST. Randomization, i.e., the use of a control group does not appear relevant. Indeed, the usual treatment for advanced Gastrointestinal Stromal Tumors Refractory to Imatinib and Sunitinib is best supportive care for which outcome data are already available (Demetri et al., 2012; Italiano et al., 2012).
Sixty three patients will be included in 10 centres of the French Sarcoma Group over a period of 18 months of enrolment.

4. Population

4.1 Patient population

Adult patients with documented disease progression 2nd line sunitinib for unresectable and/or metastatic GIST.
Written informed consent is obtained prior to any screening procedures. The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered enrolment in the study.

4.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet all of the following criteria:

1. Male or female patients ≥ 18 years of age
2. Histologically confirmed GIST of any anatomical location and confirmed by the RRePS Network ; positive immunohistochemical staining for c-KIT (CD117); or negative staining for KIT, but with either positive staining for DOG1 or an identified mutation of *KIT* or *PDGFRA* gene
3. Homozygous or heterozygous *CDKN2A* gene deletion assessed by array-comparative genomic hybridization (array-CGH)
4. Unresectable and/or metastatic disease with documented progression according to modified RECIST criteria (see section 7.2.1.5) after 1st line imatinib and 2nd line sunitinib. Progression on the last line of treatment should be confirmed by central review with two radiological assessments identical (CT scans or MRI) obtained at less from 4 months interval within the 24 months before inclusion.
5. At least one measurable GIST lesion according to RECIST (v1.1 Appendix 3). A previously irradiated lesion is eligible to be considered as a measurable lesion provided that there is objective evidence of RECIST progression of the lesion prior to starting PD-0332991.

6. A performance status of 0, 1 or 2 according to the Eastern Cooperative Oncology Group (ECOG) scale(Appendix 1)
7. Recovery from Grade 2 to 4 toxicity related to prior line of treatment assessed according to NCICTCAE v.4.0 (Appendix 2)
8. Adequate bone marrow function as shown by:
   - Blood absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   - Blood platelets ≥ 100 x 10^9/L
   - Blood hemoglobin (Hgb) > 9 g/dL
9. Adequate liver function as shown by:
   - Serum or plasma ALT and AST ≤ 3.0 x ULN (regardless of the presence or absence of metastases)
   - Serum or plasma total bilirubin: ≤ 1.5 x ULN (excepted for patients with Gilbert's syndrome)
10. Adequate renal function as shown by serum creatinine ≤ 2 x ULN
11. Patients who give a written informed consent obtained according to French and European regulations.
12. Patients affiliated to the French Social Security

4.3 Exclusion criteria

1. Homozygous *RB1* gene deletion assessed by array-comparative genomic hybridization (array-CGH)
2. Patients who received anti-cancer drugs ≤ 5 days prior to starting PD-0332991
3. Patients who are treated or planned to be treated concomitantly with other cytotoxic or antineoplastic treatments, such as chemotherapy, immunotherapy, biological response modifiers, or radiotherapy
4. Patients with another primary malignancy within 2 years prior to starting the study drug, with the exception of adequately treated in-situ carcinoma of the uterine cervix, or completely excised (R0 resection) basal or squamous cell carcinoma of the skin
5. Patients with a corrected QT interval using Bazett's formula (QTcB) > 470 msec.
6. Current use or anticipated need for food or drugs that are known strong cytochrome P450 (CYP)3A4 inhibitors (i.e. grapefruit juice, verapamil, ketoconazole, miconazole, itraconazole, posaconazole, erythromycin, clarithromycin, tilithromycin, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir, nefazodone, diltiazem, and delaviridine)
7. Patients with impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of PD-0332991 (e.g. severe ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or extensive (>1m) small bowel resection, inability to swallow oral medications). Prior partial gastrectomy is not an exclusion criterion.
8. Patients with prior complete gastrectomy
9. Any of the following in the previous 6 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism.
10. Patients with any clinically significant medical or surgical condition which, according to investigators' discretion, should preclude participation - i.e. active or uncontrolled infection, uncontrolled diabetes, active or chronic liver disease

(cirrhosis, chronic active hepatitis or chronic persistent hepatitis) - hepatitis B or C virus carriers with normal liver function tests, can be included

11. Known diagnosis of human immunodeficiency virus (HIV) infection. HIV testing is not mandatory
12. Patients who are currently receiving anticoagulation treatment with therapeutic doses • of warfarin or equivalent anticoagulant (e.g. high dose aspirin or clopidogrel or other) • or have an INR >1.5. Treatment with acetylsalicyclic acid 100 mg daily or low molecular weight heparin (LMWH) is allowed
13. Pregnant or breast-feeding women
14. Women of child-bearing potential not employing two effective methods of birth control. Effective contraception must be used throughout the trial and 24 weeks after the end of PD-0332991 (e.g. condom with spermicidal jelly, foam suppository or film; diaphragm with spermicide; male condom and diaphragm with spermicide, oral, implantable, or injectable contraceptives). Women of child-bearing potential defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months (i.e. who has had menses any time in the preceding 12 consecutive months), must have a negative serum pregnancy test ≤ 21 days prior to starting study drug.
15. Fertile males not willing to use contraception as stated above
16. Patients unwilling or unable to comply with the protocol.

5. Plan of study

5.1 Duration of Study

- Beginning of inclusion: January 2014
- Inclusion period: January 2014 to June 2017 (42 months)
- Length of patient participation: 18 months
- Study length: 60 months

5.2 Duration of treatment

Patient must provide a signed Informed Consent Form (ICF) (Appendix 14) prior to any study specific screening evaluations. Table 5 lists study procedures to be completed at the baseline screening visit. The screening/baseline visit will occur from -21 to -1 days prior to the Day 1 of the first dose of PD-0332991.

Patients will be evaluated at scheduled visits in up to three study periods:

- Pre-treatment (PRE TT): from signature of informed consent to the first treatment by PD-0332991.
- Treatment (TT): from the first treatment by PD-0332991 to the first 28 days following the last PD-0332991 administration.
- Follow-up (FUP): after treatment discontinuation, all patients must be followed up for 28 days after the last dose of the study drug for safety assessment (AEs and/or SAEs).

Patients will be considered to be on-study from the signature of the informed consent to the end of follow-up period.

5.3 Survival data collection

All patients will be followed up every 3 months for survival for one year after the end of treatment and information will be documented in the source documents and in CRF.

5.4 Definition of end of the study

The study end (Last Patient Last Visit) is planned by December 2017.
Patients will be followed for progression or survival. Any patient who is discontinued from PD-0332991 for any reason (except for death, disease progression, lost to follow-up, subject/guardian decision [withdrawal of consent], or study termination) will continue to have tumor assessments performed every 3 months until radiological progression, start of new anticancer therapy or death

5.5 Protocol Deviations

A protocol deviation is defined as any departure from what is described in the protocol of a clinical trial approved by an Independent Ethics Committee/Institutional Review Board (IEC/IRB) and Competent Authorities. Therefore, this applies to deviations related to patient inclusion and clinical procedures (e.g., assessments to be conducted or parameters to be determined), and also to other procedures described in the protocol that concern the Good Clinical Practice (GCP) guidelines or ethical issues (e.g., issues related to obtaining the patients' Informed Consent, data reporting, the responsibilities of the investigator, etc.).

Deviations with no effects on the risk/benefit ratio of the clinical trial (such as minimal delays in assessments or visits) will be distinguished from those that might have an effect on this risk/benefit ratio, such as:

- Deviations that might affect the clinical trial objectives, such as those involving the inclusion/exclusion criteria (which could mean that the patient is not eligible for the trial) and those having an effect on patient evaluability.
- Deviations that might affect the patient's well-being and/or safety, such as an incorrect dosing of the investigational medicinal product (PD-0332991) due to not following dose adjustment specifications.
- Deviations related to the following of GCP guidelines as described in the protocol and regulations in force, such as deviations when obtaining the Informed Consent or not following the terms established for reporting serious adverse events, etc.

❖ ***Process schedule of protocol deviation:***

The investigators may suggest to the Sponsor by email for the authorization of certain protocol deviations, especially if they are related to the inclusion/exclusion criteria or if they may have an effect on the evaluability of the patients. As a general rule, NO deviations that may have an effect on the risk/benefit ratio of the clinical trial will be authorized. Protocol deviations considered particularly relevant, which are related to ethical issues, fulfillment of GCP guidelines and trial procedures, will be notified to the pertinent IEC/IRB and, if pertinent, to the relevant authorities as established by local regulations.

Contact to request protocol deviation:

David JUZANX (CRA)
Mail: d.juzanx@bordeaux.unicancer.fr - Tel : + 33 5 24.07.19.25
or Sabrina SELLAN-ALBERT (CRA Back-up), Mail – s.albert@bordeaux.unicancer.fr)

The sponsor will send by email the response of requested deviation.

5.6 Replacement of patients

Patients must be replaced if they are considered not fully evaluable for the assessment of the primary endpoint due to following circumstances:

- They are withdrawn from the study before receiving any administration of PD-0332991 on the first day (Day 1) of the first cycle of the scheduled treatment (“evaluable cycle”), OR
- They did not receive at least one complete or two incomplete treatment cycles of PD-0332991 OR
- There is a protocol deviation resulting in an impossibility of concluding anything regarding the antitumor activity of PD-0332991 (e.g.: disease is not measurable as per RECIST or disease is only measurable within a previous irradiated field, CNS involvement, progressive disease at inclusion not confirmed by central review) OR
- Patients who received at least one administration of PD-0332991 AND unrelated AEs AND without any tumor assessments after the start of study treatment OR
- Patients who received at least one administration of PD-0332991 AND who refused to continue on study for any reason AND without any tumor assessments after the start of study treatment

However, any patient who received at least one administration of PD-0332991 will be included in the safety analysis.

6. Treatment

6.1 Investigational treatment, other study treatment, supportive treatment

6.1.1 Dosing regimen

Table 1 Dose and treatment schedule

Study Treatment	Pharmaceutical Form and Route of Administration	Dose	Frequency and/or Regimen
PD-0332991	Capsule, oral use	125 mg	Daily 21 days on/7 days off (28 day cycles)

PD-0332991 dosed on a flat scale of 125 mg will be administrated orally o.d on a 21 days on / 7 days off dosing schedule. One cycle is considered to consist of 4 weeks of PD-0332991 administration.
Patients should be instructed to administrate PD-0332991 with a sufficient amount of water at least 1 hour prior to a meal or at least 2 hours following a meal and to swallow the required number of capsules at approximately the same time on each day.
If the patient forgets to take the study treatment as described, he/she should skip the dose for that day and resume taking the PD-0332991 on the next scheduled day.
The investigator or designee must instruct the patient to take PD-0332991 exactly as prescribed. All study treatments prescribed and dispensed to the patient and all dose changes during the study must be recorded on the CRF.
Patients must be advised to bring their unused PD-0332991 capsules to the investigational site at each visit.

6.1.2 Ancillary treatments

In addition to receiving PD-0332991, all patients should receive best supportive care (BSC), as per standard local practice for the treatment of pre-existing medical conditions or adverse events that may arise during the study. BSC is defined as drug or non-drug therapies, nutritional support, physical therapy or any other treatment alternative that the investigator believes to be in the patient's best interest, but excluding other antineoplastic treatments. All medications and non-drug therapies (including physical therapy, oxygen and blood transfusions) administered to the patient prior (within 28 days of the first dose of PD-0332991 or during the course of the study, and until 28 days after the last dose of PD-0332991 must be reported on CRF.
Patients must be instructed not to take additional medications (including over-the-counter products and herbal/alternative medications during the study without prior consultation with the investigator).

Permitted treatments during the study include, but are not limited to the following:
• Pain medication to allow the patient to be as comfortable as possible
• Nutritional support or appetite stimulants (e.g. megestrol)
• Oxygen therapy and blood products or transfusions
• Prophylactic anti-emetics are allowed for patients who, at the discretion of the investigator, have experienced ≥ grade 1 nausea or vomiting
• Hematopoietic growth factors should be used according to investigator practice.

• Concurrent use of other investigational drugs is not permitted

• The administration of other antineoplastic therapy (e.g. chemotherapy, hormone therapy, immunotherapy, targeted therapy, monoclonal antibodies and radiation therapy) is not permitted. Patients requiring radiation therapy after the start of the study are considered as having progression of disease and must discontinue study treatment.

6.2 Treatment duration

Patients will be treated with PD-0332991 until progression of disease, unacceptable toxicity, death or discontinuation for any other reason.

6.3 Dose modifications

6.3.1 Dose modification and dose delay

If the patient forgets to take the study treatment as described, he/she should skip the dose for that day and resume taking the PD-0332991 on the next scheduled day.
For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. The following guidelines need to be applied.

Table 2 : Dose reduction*			
	Starting dose level - 0	Dose level - 1	Dose level - 2
PD-0332991	125 mg	100 mg	75 mg
*Dose reduction should be based on the worst toxicity demonstrated at the last dose. **Dose reduction below 75 mg is not allowed.			

6.3.2 Treatment interruption and treatment discontinuation

6.3.2.1 ***Interruption***

If the administration of PD-0332991 must be interrupted because of an unacceptable toxicity, study drug dosing will be interrupted or modified according to rules described in Table 3. A patient who requires a dose interruption (regardless of the reason for the interruption) lasting > 28 days (counting from the first day when a dose was missed) must discontinue PD-0332991. All treatment interruption must be recorded on the CRF.

Patients whose treatment is interrupted due to an adverse event or abnormal laboratory value must be followed at least once a week for 28 days and subsequently at 28 day intervals, until resolution or stabilization of the event, whichever comes first.

6.3.2.2 ***Discontinuation***

PD-0332991 will be discontinued for any of the following reasons:
• Disease progression
• Consent withdrawal
• Unacceptable adverse events
• Major violation of the protocol
• A dose interruption of > 28 days or a dose delay of > 28 days from the intended day of the next scheduled dose
• Intercurrent illness that prevent further administration of treatment
• Pregnancy
• Need for any other types of anticancer therapy

• General or specific changes in the patient's condition which render the patient unacceptable for further treatment at the discretion of the investigator
• Lost to follow-up
• Death.

If PD-0332991 is permanently discontinued, the patient will be considered to have completed study treatment. All patients must have safety evaluations for 28 days after the last dose of PD-0332991.

Patients who discontinue PD-0332991 should be scheduled for an End of Treatment Visit, whenever possible, after discontinuing PD-0332991, at which time all of the assessments listed for the End of Treatment Visit will be performed. The date and reason for stopping the study treatment should be recorded on the CRF.

Table 3 : Criteria for dose adjustment, interruption and re-initiation of PD-0332991	
Worst Toxicity CTCAE v4.0 Gradea unless otherwise specified (Value)	During a cycle of therapy
No toxicity	Maintain dose level
Hematologic	
Neutropenia (ANC)	
Grade 1 – 2	Maintain dose level
Grade 3 – 4	Delay PD-0332991 until resolved to ≤ grade 2, then: If resolved by ≤ 7 days after suspending PD-0332991 , maintain dose level If resolved by > 7 days after suspending PD-0332991 ↓ 1 dose level
Thrombocytopenia	
Grade 1 – 2	Maintain dose level
Grade 3	Delay PD-0332991 until resolved to ≤ grade 1, then: If resolved by ≤ 7 days after suspending PD-0332991 , maintain dose level If resolved by > 7 days after suspending PD-0332991 ↓ 1 dose level
Grade 4	Delay PD-0332991 until resolved to ≤ grade 1, then ↓ 1 dose level
Febrile neutropenia (Grade 3 or 4)	Delay PD-0332991 until resolved, then ↓ 1 dose level
Cardiac - Prolonged QTc interval	
During cycle 1	
No QTcF change from baseline > 60 msec	Maintain dose level and ECG monitoring as specified for subsequent cycles in Table 5.
QTcF change from baseline > 60 msec (but absolute QTcF < 500 msec)	Maintain dose level. ECG monitoring assessments will be performed every week for 4 weeks, and then every two weeks for the next 8 weeks. After 12 weeks, ECGs will be performed as indicated for subsequent cycles in Table 5, or more frequently as clinically indicated by the investigator.

During any cycle	
QTcF ≥ 500 msec as identified by the investigator on the automated site ECG reading	For all patients with a new absolute QTcF ≥ 500 msec duration, occurring at any time during study, as identified by the investigator on the automated site ECG reading, an immediate evaluation of that ECG will be obtained and if confirmed (QTcF ≥ 500), then dosing with PD-0332991 will be suspended. The Sponsor should be notified immediately. The patient will be hospitalized or monitored by the investigator with hourly ECGs until the QTcF has returned to < 30 msec from baseline. Immediate attention to potassium, magnesium, and other clinical factors such as oxygenation, ischemia, and the like will be addressed. Once QTc prolongation has resolved, patients may be re-treated at the next lower dose level with frequent ECG monitoring. If the ECGs obtained in the first cycle after dose reduction are without any QTcF change from baseline > 60 msec, then ECG monitoring will be performed as indicated in Table 5 for all subsequent cycles. If, in the first cycle after dose reduction the patient had a QTcF change from baseline > 60 msec, but absolute QTcF < 500 msec, then ECG monitoring will be performed every week for 4 weeks, and then every two weeks for the next 8 weeks. After 12 weeks, ECGs will be performed as indicated for subsequent cycles in Table 5, or more frequently as clinically indicated by the investigator. Patients who experience absolute QTcF ≥ 500 msec after dose reduction will be discontinued from study.
Diarrhea	
Grade 1 (despite maximal antidiarrheal medication)	Maintain dose level
Grade 2 (despite maximal antidiarrheal medication)	Delay PD-0332991 until resolved to ≤ grade 1, then re-start at the current dose level. If diarrhea returns as ≥ grade 2, then suspend dose until resolved to ≤ grade 1, then ↓ 1 dose level
Grade 3 or 4 (despite maximal	Delay PD-0332991 until resolved to ≤

antidiarrheal medication)	grade 1, then ↓ 1 dose level
Nausea (Suspend dose for CTCAE grade 2-3 nausea only if it could not be controlled despite the use of standard anti-emetics.)	
Grade 1 (despite standard anti-emetics)	Maintain dose level
Grade 2 (despite standard anti-emetics)	Delay PD-0332991, until resolved to ≤ grade 1, and then re-start at the current dose level. If nausea returns as ≥ grade 2, then suspend dose until resolved to ≤ grade 1, then ↓ 1 dose level.
Grade 3-4 (despite standard anti-emetics)	Delay PD-0332991 until resolved to ≤ grade 1, then ↓ 1 dose level
Vomiting (Suspend dose for CTCAE grade 2-4 vomiting only if it could not be controlled despite the use of standard anti-emetics.)	
Grade 1 (despite standard anti-emetics)	Maintain dose level
Grade 2 (despite standard anti-emetics)	Delay PD-0332991, until resolved to ≤ grade 1, and then re-start at the current dose level. If vomiting returns as ≥ grade 2, then suspend dose until resolved to ≤ grade 1, then ↓ 1 dose level.
Grade 3-4 (despite standard anti-emetics)	Delay PD-0332991 until resolved to ≤ grade 1, then ↓ 1 dose level
Other adverse events	
Grade 1 or 2	Maintain dose level
Grade 3	Delay PD-0332991 until resolved to ≤ grade 1 or baseline, then maintain dose level or ↓ 1 dose level at the discretion of the investigator
Grade 4	Delay PD-0332991 until resolved to ≤ grade 1 or baseline, then ↓ 1 dose level or discontinue PD-0332991 at the discretion of the investigator
All dose modifications should be based on the worst preceding toxicity. Patients are allowed two dose reductions: a dose reduction from 125 mg to 100 mg, and, if necessary, a dose reduction from 100 mg to 75 mg.	

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered during the study must be listed on CRF

6.4.2 Restricted concomitant therapy

In vitro data indicate that CYP3A are mainly involved in the metabolism of PD-0332991. PD-0332991 is a weak time-dependent inhibitor of CYP3A. Concomitant administration of agents known to inhibit strongly CYP3A isoenzymes (eg, ketoconazole, miconazole, itraconazole, posaconazole, clarithromycin, erythromycin, tilithromycin, nefazodone, diltiazem, verapamil, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir, and grapefruit juice) may increase PD-0332991 exposure and should be avoid. . Concomitant administration of agents known to induce strongly CYP3A isoenzymes (e.g., phenytoin, rifampicin, carabamazepin and St-John Wort) may decrease PD-0332991 exposure and should be avoid. Moreover, concomitant use of moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, and nafcillin) should be avoid. The following website may be referenced for a more extensive list of P450 inhibitors and inducers: http://medicine.iupui.edu/clinpharm/ddis/main-table/

6.5 Study drug supply

6.5.1 *Study drug preparation and dispensation*

PD-0332991 will be provided by the designee of the sponsor to the participating site.

Table 4: Preparation and dispensing

Study Treatment	Packaging	Labeling (and dosing frequency)
PD-0332991	Capsules (125mg, 100mg, 75mg and 25 mg)	Labelled asd PD-0332991

6.5.2 Study drug packaging and labelling

PD-0332991 is formulated as gelatin capsules of 125mg, 100 mg, 75mg and 25 mg respectively. Medication labels will comply with the French legal requirements and are printed in French. The label contains PD-0332991 identifying information (e.g. formulation, batch number, and expiration date), the patient number (to be entered by the investigator or designee) and storage conditions.

6.5.3 *Drug supply and storage*

PD-0332991 is supplied by the Sponsor. It must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, PD-0332991 should be stored according to the instructions specified on the drug labels. PD-0332991 capsules should be stored at 15-30°C in a secured, limited access area.

6.5.4 *Study drug compliance and accountability*

- **Study drug compliance**

Compliance will be assessed by the investigator and/or study personnel at each patient visit.
To accurately determine the patient's drug exposure throughout the study, the following information must be reported on a patient diary (Appendix 17).

- **Study drug accountability**

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability ledger. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation. At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability ledger to the Sponsor designee provided in the investigator folder at each site.

6.5.5 **Disposal and destruction**

The drug supply can be destroyed at the local of Sponsor designee as appropriate. Destruction at the site is allowed only if permitted by French regulations and authorized by the Sponsor.

7. Visit schedule and assessments

7.1 Study flow and visit schedule

Table 5 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. All assessments have a ±3 days window unless otherwise indicated. In the event of public holiday there is a ±5 days window on all assessments. Every effort must be made to follow the schedule of assessments within the windows outlined in the protocol.

	Pre-Screening phase	Screening/Baseline	Cycle 1		Cycle N	End of Study Treatment	Survival Follow-Up
Visit Name			V1	V2	Vn		
Day of cycle		-21 to -1	Day 1	Day 15	Day 1	Within 28 days after discontinuation of study drug	
Obtain Informed Consent	X						
CDKN2A gene deletion assessed by array-CGH (centralized to Bergonie Institute)	X						
Patient history							
Demography		X					
Inclusion/exclusion		X					

criteria							
Relevant medical history/current medical conditions		X					
Diagnosis and extent of cancer		X					
Prior antineoplastic therapy		X					
Prior/concomitant medications		X	Continuous until 28 days post-late dose of study drug				
Antineoplastic therapies since discontinuation of study treatment							X
Clinical exam							
Physical examination		X	X	X	X	X	
Performance status		X	X	X	X	X	
Height/Weight		X	X	X	X	X	
Vital signs		X	X	X	X	X	
Laboratory assessments							
Hematology		X	X	X	X Days 1 and 15	X	
Chemistry		X	X	X	X	X	
Coagulation		X	X	X	X	X	
Pregnancy test		X	X		X	X	
Imaging/Other assessments							
Tumor evaluation: CT scan or MRI		Day-21 to -1	D(28) of Cycle 1, D(28) of Cycle 2 then every 8 weeks until month six and then every 12 weeks				
ECG		X	X	X	X	X	
Safety							
Adverse events			Continuous until 28 days post-late dose of study drug				
Biomarkers (Optional study)							
Tumor biopsy Day –3 to Day -1 Day 21 cycle 1		X	Day 21 Cycle 1				
Others							
PD-0332991 administration			21-days on, 7 days off				
Reason for withdrawal						X	
Survival update every 3 months for one year							X

7.1.1 Pre-Screening phase and Screening

➢ Pre-screening phase

In this study, a pre-screening is necessary to confirm homozygous or heterozygous *CDKN2A* gene deletion assessed by array-comparative genomic hybridization (array-CGH) (see section 7.1.1.3.1).

Patient must provide a signed Informed Consent Form (ICF) (Appendix 14) prior to any study specific evaluations.

➢ Screening

The screening/baseline visit will occur maximum 21 days prior to the Day 1 of first dose of study treatment PD-0332991.

The investigator must review the checklist of inclusion/exclusion criteria.

When information from procedures (for example imaging assessments) that may have been previously performed as part of the patient's routine disease care (prior to enrolling in the trial) is allowed to be used to satisfy inclusion criteria, if it was performed <21 days before the start of study treatment.

7.1.1.1 Eligibility screening

Patient's eligibility is checked locally.

7.1.1.2 Patient demographics and other baseline characteristics

The following assessments and procedures will be performed prior the start of study screening phase (see section 7.1.1.3.2):

• Obtain patient's written informed consent form

• Confirm by the RRePS Network the histological diagnosis of GIST, the positive immunohistochemical staining for c-KIT (CD117) or if negative, either positive staining for DOG1 or identified mutation on *KIT* or *PDGRA* gene

• Confirm *CDKN2A* gene deletion assessed by array-comparative genomic hybridization (array-CGH)

The following assessments and procedures will be performed within 21 days prior the start of study treatment:

• Confirm disease progression by central review (see section 7.2.1.5) after the last line of treatment.

• Radiological tumor assessment

• Demographic data and relevant medical history, current medical conditions

• Prior antineoplastic therapies

• Cardiovascular assessment
  - Electrocardiogram (ECG)

• Physical examination
  - Vital signs
  - Height and weight
  - Performance status

• Laboratory investigations:
  - Hematology: hemoglobin, platelet count, a complete red blood cell count (RBC), total white blood count (WBC) with differential (total neutrophil

[including bands], lymphocyte, monocyte, eosinophil, and basophil counts).
- Coagulation: Prothrombin time (PT, described as INR) and APTT
- Chemistry : urea/BUN, creatinine, calcium, sodium, magnesium, potassium, phosphorous, fasting glucose, albumin, total bilirubin, alkaline phosphatase, GGT, AST, and ALT, LDH, amylase, lipase and triglycerides.

• Biomarkers collection (optional study): Tumor biopsy at Day –3 to Day -1
• Pregnancy test if applicable: serum blood of pregnancy test

7.1.1.3 **Patient registration**

7.1.1.3.1 **Pre-Screening phase :**

Upon signature of consent, screened patient will be entered on study centrally at the Bergonie Institute Coordinating Center by the Study Coordinator.
The **following documents should be faxed or e-mail** as soon as possible to the Bergonie Institute Data Center:
_ Pre-Screening form (Appendix 7):
- ✓ Institution number
- ✓ Name of the responsible investigator
- ✓ Patient's code (2 letters of name, 2 letters of first name)
- ✓ Patient's birth date (day/month/year)
- ✓ Date of signed consent form
- ✓ Date of signed consent form for optional study , if applicable

Clinical Trial and Epidemiology Unit – Institut Bergonie- Protocol CYCLIGIST
FAX : +33 5 56 33 04 85
From Monday through Friday - From 9.00 am to 5.00 pm
Contact : David JUZANX - Tel : + 33 5 24.07.19.25 – Mail: d.juzanx@bordeaux.unicancer.fr
and Sabrina SELLAN-ALBERT (CRA Back-up), Mail – s.albert@bordeaux.unicancer.fr

Each site will send to Bergonie Institute within 7 Days after signature of informed consent:
- Pathology request form completed (Appendix 9)
- FFPE (Formalin-Fixed Paraffin-Embedded) of initial block of specimen tumor sampling (see section 7.2.1.3)
- Initial pathology report with patient code and date of birth (including macroscopic description) and pathology report of molecular biology(see section 7.2.1.4)

To complete the registration process, the Coordinator will assign a patient pre-screening number.
Upon results of pathological will be available, (see section 7.2.1.4) the CRA at Bergonie Institute should inform site by e-mail and/or fax and return results.

In case of an array-comparative genomic hybridization (array-CGH) to assessed homozygous or heterozygous *CDKN2A* gene deletion is already done, each site will send to Bergonie Institute the informatics file corresponding of genomic profile. A

validation is necessary by Department of tumoral genetic pathology, F.Chibon and collaborators, Bordeaux, France.

7.1.1.3.2 ***Screening phase:***

Upon confirmation of pre-screening results are positive (see section 7.1.1.3.1), the investigator must review the checklist of inclusion/exclusion criteria.

In case of pre-screening results are negative, patient will be on screening failures.

The screening/baseline visit will occur maximum 21 days prior to the Day 1 of first dose of study treatment PD-0332991.

Each site will send to Bergonie Institute for central review before registration (see section 7.2.1.5.2):

- Anonymized CD of CT-scan or MRI of two radiological assessments identical obtained at less from 4 months interval within the 24 months before inclusion
- "Baseline Clinical Subject Profile" (Appendix 11) with the first shipment.
- "Radiology Referral Form" (Appendix 12).

Upon results of radiological assessment, the CRA at Bergonie Institute should inform site by e-mail and/or fax and return results.

7.1.1.3.3 ***Inclusion***

With pre-screening and screening results, all eligible patients will be registered on study centrally by the Study Coordinator.

To register a patient, **the following documents should be faxed or e-mail** to the Bergonie Institute Data Center:

_ Registration form (Appendix 8):

- ✓ Institution number
- ✓ Name of the responsible investigator
- ✓ Patient's code (2 letters of name, 2 letters of first name)
- ✓ Patient's birth date (day/month/year)
- ✓ Pre-Screening number
- ✓ Eligibility criteria
- ✓ Data foreseen for protocol treatment start

Clinical Trial and Epidemiology Unit – Institut Bergonie- Protocol CYCLIGIST
FAX : +33 5 56 33 04 85
From Monday through Friday - From 9.00 am to 5.00 pm
Contact : David JUZANX - Tel : + 33 5 24.07.19.25 – Mail: d.juzanx@bordeaux.unicancer.fr
and Sabrina SELLAN-ALBERT (CRA Back-up), Mail – s.albert@bordeaux.unicancer.fr

This must be done **before the start of the protocol treatment which should begin within one week (7 days) following registration**.

To complete the registration process, the CRA will:

_ Assign a patient study number
_ Register the patient on the study
_ Fax and/or e-mail the patient study number

The patient study number attributed at the end of the registration procedure identifies the patient and must be reported on all case report forms.

7.1.2 *Treatment period*

Patients will receive PD-0332991 after the last line of treatment washout period of at least 5 days, on an outpatient basis at the dose of 125 mg qd for 21 days followed by 7 days off, for cycle of 4 weeks (28d) until disease progression–documented by RECIST v1.1 (Appendix 3), unacceptable toxicity, or consent withdrawal. Patients will be required to swallow the required number of capsules of PD-0332991 at approximately the same time on each dosing day, with sufficient amount of water and at least 1 hour prior to a meal and at least 2 hours following a meal. If a dose is missed for any reason, including vomiting, patients should resume taking the study medication with the next scheduled day.

The following assessments and procedures will be performed prior the start of study treatment:

- Current medical conditions
- Radiological tumor assessment by CT Scan or MRI: D(28) of Cycle 1, D(28) of Cycle 2 then every 8 weeks until month six and then every 12 weeks
- Cardiovascular assessment
    - Electrocardiogram (ECG)
- Physical examination
    - Vital signs
    - Weight
    - Performance status
- Laboratory investigations:
    - Hematology: hemoglobin, platelet count, a complete red blood cell count (RBC), total white blood count (WBC) with differential (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts).
    - Coagulation: Prothrombin time (PT, described as INR) and APTT
    - Chemistry : urea/BUN, creatinine, calcium, sodium, magnesium, potassium, phosphorous, fasting glucose, albumin, total bilirubin, alkaline phosphatase, GGT, AST, and ALT, LDH, amylase, lipase and triglycerides.
- Biomarkers collection (optional): Tumor biopsy at Day 21 cycle 1
- Pregnancy test if applicable: serum blood of pregnancy test

All assessments have a ±3 days window unless otherwise indicated. In the event of public holiday there is a ±5 days window on all assessments. Every effort must be made to follow the schedule of assessments within the windows outlined in the protocol.

7.1.3 *End of treatment visit, including premature withdrawal and study discontinuation visit*

Patients who discontinue PD-0332991 for any reason should be scheduled for a visit within 28 days after discontinuation of study drug.

The following assessments and procedures will be performed:

- Current medical conditions

- Radiological tumor assessment
- Cardiovascular assessment: electrocardiogram (ECG)
- Physical examination
- Vital signs
- Weight
- Performance status
- Laboratory investigations:
    - Hematology: hemoglobin, platelet count, a complete red blood cell count (RBC), total white blood count (WBC) with differential (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts).
    - Coagulation: Prothrombin time (PT, described as INR) and APTT
    - Chemistry : urea/BUN, creatinine, calcium, sodium, magnesium, potassium, phosphorous, fasting glucose, albumin, total bilirubin, alkaline phosphatase, GGT, AST, and ALT, LDH, amylase, lipase and triglycerides.
- Pregnancy test if applicable: serum blood of pregnancy test

An End of Treatment CRF page should be completed, giving the date and reason for stopping the study treatment. At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 28 days following the last dose of study treatment.

If a study withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the End of Treatment CRF page.

If a patient discontinues study treatment, but continues study assessments, the patient remains on study until such time as he/she completes protocol criteria for ending study assessments.

At that time, the reason for study completion should be recorded on the CRF.

7.1.4 *Follow up period*

All patients must be followed up for 28 days after the last dose of study drug for safety assessment (AEs and/or SAEs).

Patient who discontinued study drug for disease progression, a follow-up survival update must be done every 3 months during a year, until death or study termination.

Any patient who is discontinued from PD-0332991 for any reason (except for death, disease progression, lost to follow-up, subject/guardian decision [withdrawal of consent], or study termination) will continue to have tumor assessments performed every 3 months until radiological progression, start of new anticancer therapy or death.

All new anticancer therapies given after the last dose of the study drug PD-0332991 will be recorded on CRF pages designed to capture antineoplastic therapies since discontinuation from the study.

7.2 Assessment types

7.2.1 *Diagnosis*

7.2.1.1 Diagnosis of GIST

Diagnosis of Gastro Intestinal Stromal Tumor (GIST) must be histologically confirmed of any anatomical location; positive immunohistochemical staining for c-KIT (CD117); or negative staining for KIT, but with either positive staining for DOG1 and an identified mutation of *KIT* or *PDGFRA* gene

If diagnosis of GIST was not confirmed by the RRePS Network (Appendix 16), missing analysis will be performed by Bergonie Institute, Pr. Coindre and collaborators, Department of Pathology, Bordeaux, France. The reviewer will assess pathological diagnosis, document the results on the "Pathology request form" response completed (Appendix 9) and sign this form.
Every discrepancy will be discussed between referral investigator, principal investigator, Pr. Coindre or collaborators and medical responsible from the Sponsor, until a final decision is reached.
Patients with pathological diagnosis different from GIST after central review will be considered ineligible and will not be included in the study.

7.2.1.2 ***Array-CGH analysis***

The analysis of *CDKN2A* gene deletion assessed by array-comparative genomic hybridization (array-CGH) will be performed by Bergonie Institute, Department of tumoral genetic pathology, F.Chibon and collaborators, Bordeaux, France.

7.2.1.3 ***Pathological specimen sampling necessary to array-CGH analysis***

Available tumor samples obtained at diagnosis or at relapse, FFPE (Formalin-Fixed Paraffin-Embedded) of block is mandatory to analysis CDKN2A gene deletion.

7.2.1.4 ***Array-CGH analysis process schedule and practical implementation***

Each site will send to Bergonie Institute within 7 Days after signature of informed consent:

- Pathology request form completed (Appendix 9)
- FFPE (Formalin-Fixed Paraffin-Embedded) of block of specimen tumor sampling
- Initial pathology report with patient code and date of birth (including macroscopic description) and pathology report of molecular biology

➢ Pr. Coindre and collaborators, Department of Pathology Bordeaux France, will assess homozygous or heterozygous *CDKN2A* gene deletion, document the results on the "Pathology request form" response completed (Appendix 9) and sign this form.

All Pathological specimens sampling with documents must be sent to:

Institut Bergonié-Service Pathologie-
Technicienne Anapath Recherche Clinique
Protocole CYCLIGIST
229 cours de l'Argonne-33076 Bordeaux Cedex, France
Tél: 05.56.33.78.53

❖ In case of an array-comparative genomic hybridization (array-CGH) to assessed homozygous or heterozygous *CDKN2A* gene deletion is already done, each site will send to Bergonie Institute the informatics file corresponding of genomic profile. A validation is necessary by Department of tumoral genetic pathology,

F.Chibon and collaborators, Bordeaux, France and signed by Pr. Coindre and collaborators, Department of Pathology Bordeaux France.

7.2.1.5 Diagnosis of Progressive Disease – central review before registration

Centralized radiological review will be performed to confirm progressive disease status at inclusion time. Progressive disease should be confirmed according to RECIST 1.1 modified as follows for the purpose of this study: no lymph nodes will be chosen as target lesions—no bone lesions will be chosen as target lesions. Additionally a progressively growing new tumour nodule within a pre-existing tumour mass have to meet the following criteria to be regarded as unequivocal evidence of progression according to our modification to RECIST 1.1: the lesion is at least 2 cm in size and definitely a new active GIST lesion (eg, enhanced with contrast or other criteria to rule out artefact); or the lesion have to be expanding on at least two sequential imaging studies.
This will be performed by centrally reviewing two radiological assessments identical (CT scans or MRI) obtained at less from 4 months interval within the 24 months before inclusion

7.2.1.5.1 ***General procedure***

Review process will be centralized at Bergonie Institute and will be performed by one radiologist expert in Gastro Intestinal Stromal Tumor.
The results of the centralized radiological review will be used for the diagnosis of progressive disease.

7.2.1.5.2 ***Review process schedule and practical implementation at baseline***

With regards to inclusion scan, the progressive disease status at baseline must be confirmed by central review.

- Each site will send two-imaging CD (two radiological assessments identical (CT scans or MRI) obtained at less from 4 months interval within the 24 months before inclusion) to Institut Bergonié
- Each site must send the completed “Baseline Clinical Subject Profile” (Appendix 11) with the first shipment.
- For each shipment, each media should be accompanied by the completed “Radiology Referral Form” (Appendix 12).

➢ The reviewer will assess baseline status, document the results on the “Baseline Radiology Review Form” (Appendix 13) and sign this form.

Patient’s information must be recorded on an imaging CD.
All CDs and document must be sent to:

David Juzanx
Clinical Research Assistant
Institut Bergonié – 229 cours de l’Argonne – 33076 Bordeaux Cedex, France
Phone: +33 5 24 07 19 25 – Mail: d.juzanx@bordeaux.unicancer.fr

7.2.2 Efficacy assessments

Tumor assessment and response will be assessed according to RECIST (version 1.1-Appendix 3), with same type of exam in regard of baseline.

All potential sites of tumor lesions (target and non-target lesions) will be assessed using MRI or CT Scan with IV contrast of the Thorax Abdomen and Pelvis using a 5mm slice thickness with a contiguous reconstruction algorithm (a PET scan is not acceptable for radiological evaluation).

Evaluation will be assessed:

- at baseline within 21 days before the first dose of PD-0332991
- at D(28) of Cycle 1, at D(28) of Cycle 2 then every 8 weeks until month six and then every 12 weeks until disease progression or starting other treatment. A time window of 7 days is allowed for the radiologist to give his/her statement.

Clinical suspicion of disease progression at any time requires a physical examination and radiological confirmation to be performed promptly rather than waiting for the next scheduled radiological assessment.

Response regarding the first endpoint will be assessed by central radiology review.

Whenever the criteria of response are met (Complete Response (CR) or Partial Response (PR)), the appropriate imaging tests will be repeated at least four weeks later in order to confirm the response.

The decision regarding patient management will remain with the local investigator.

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions. The investigator and/or the local radiologist selects the target (a bone lesion is not acceptable for a target lesion) and non-target lesions at baseline and follows each of the selected lesion (s) at each subsequent tumor assessment until the patient presents with disease progression.

All patients should have at least one measurable lesion (nodal or non-nodal) by CT scan or MRI.

For optimal evaluation of patients the same methods of tumor assessment and technique (CT scan with contrast or MRI) should be used to characterize each identified and reported lesion at baseline and during follow-up. A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI), or a change in any other imaging modality.

Moreover, a new nodule within a preexisting tumor mass will be considered as unequivocal evidence of progression when the lesion is at least 2 cm in size and radiologically compatible with a GIST lesion, or the lesion is growing in at least 2 successive scans/MRI and radiologically compatible with a GIST lesion.

In addition to RECIST v1.1 (Appendix.3) evaluation, all subject data acquired using contrast-enhanced CT will be evaluated according to Choi criteria. (Appendix.4) Choi reading will be performed locally.

❖ ***Review process schedule and practical implementation at first end point***

With regards to inclusion scan, the response regarding the first endpoint will be assessed by central radiology review

- Each site will send imaging CD (radiological assessments identical (CT scans or MRI) obtained at each evaluation) to Institut Bergonié
- For each shipment, each media should be accompanied by the completed “Radiology Referral Form” (Appendix 12).

Patient's information must be recorded on an imaging CD.
All CDs and document must be sent to:

David Juzanx
Clinical Research Assistant
Institut Bergonié – 229 cours de l'Argonne – 33076 Bordeaux Cedex, France
Phone: +33 5 24 07 19 25 – Mail: d.juzanx@bordeaux.unicancer.fr

7.2.3 *Safety and tolerability assessments*

Safety will be monitored by assessing all adverse events, including serious adverse events, the regular monitoring of hematology, blood chemistry, cardiac assessments and regular monitoring of vital signs and physical condition. These assessments should be performed ± 3 days of the scheduled day of assessment except for adverse events that will be evaluated continuously through the study (Refer to Table 5).

Scheduling of safety assessments for PD-0332991 cannot be changed due to dose interruptions. Refer to Section 6.3 for permitted PD-0332991 adjustments as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 10.2.

7.2.3.1 ***Physical examination***

A complete physical examination includes a major review of body systems (general appearance, skin, neck including thyroid, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities), a neurological examination only performed at baseline.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to start PD-0332991 must be included in the CRF. Significant findings made after starting PD-0332991 which meet the definition of an Adverse Event must be recorded on the Adverse Event CRF pages.

A physical examination will be performed and recorded in source documents at:

• Baseline ≤ 21 days prior to the first dose of PD-0332991
• Days 1 and 15 in cycle 1
• Day 1 in subsequent cycles
• End of treatment
• As clinically indicated.

7.2.3.2 ***Vital signs***

Vital signs will be recorded on the appropriate CRF pages. Body temperature, sitting pulse rate, and sitting blood pressure will be measured at each visit. Vital signs will be measured at:

• Baseline ≤ 21 days prior to the first dose of PD-0332991
• Days 1 and 15 in cycle 1
• Day 1 in subsequent cycles
• End of treatment
• As clinically indicated.

Vital signs are measured according to normal medical practice.

7.2.3.3 ***Height and weight***

Height will be measured only at screening. Height will be measured in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes).

Weight will be measured at:

• Baseline ≤ 21 days prior to the first dose of PD-0332991
• Days 1 and 15 in cycle 1
• Day 1 in subsequent cycles
• End of treatment
• As clinically indicated.

7.2.3.4 ***Performance status***

The performance status will be scored using the ECOG Performance Status assessment scales (Appendix 1)

Performance status will be assessed at:

• Baseline ≤ 21 days prior to the first dose of the study treatment
• Days 1 and 15 in cycle 1
• Day 1 in subsequent cycles
• End of treatment
• As clinically indicated.

7.2.3.5 ***Laboratory evaluations***

Laboratory evaluations must be performed locally at every protocol required visit (Table 5) or as frequently as clinically indicated.

If the baseline laboratory assessments occurred within 48 hours of cycle 1 day 1, the laboratory evaluation does not need to be repeated at that time.

- *Hematology*

Hematology tests include hemoglobin, platelet count, a complete red blood cell count (RBC), total white blood count (WBC) with differential (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts).

Hematological tests will be performed at:

• Baseline ≤ 21 days prior to the first dose of PD-0332991
• Days 1 and 15 in cycle 1
• Day 1 and Day 15 in subsequent cycles
• End of treatment and study
• As clinically indicated.

If the baseline blood sample collection occurred within the previous 48 hours of cycle 1 day 1, the hematology does not need to be repeated at that time.

In case of hematological toxicities > Grade 2 that require study treatment modifications or interruptions, hematological tests should be repeated until recovery to the baseline value or ≤ grade 2. Refer to Table 3 for PD-0332991 treatment adjustments

- *Coagulation*

Prothrombin time (PT, described as INR) and APTT are examined as coagulation assessments.

They will be performed at:

• Screening
• Days 1 and 15 in cycle 1
• Day 1 in subsequent cycles
• End of treatment and study
• As clinically indicated.

If the baseline blood sample collection occurred within the previous 48 hours of cycle 1 day 1, the coagulation assessments do not need to be repeated at that time.

- *Clinical chemistry*

Biochemistry consists of urea/BUN, creatinine, calcium, sodium, magnesium, potassium, phosphorous, glucose, albumin, total bilirubin, alkaline phosphatase, GGT, AST, and ALT, LDH, amylase, lipase and triglycerides.

• Baseline ≤ 21 days prior to the first dose of PD-0332991
• Days 1 and 15 in cycle 1
• Day 1 in subsequent cycles
• End of treatment and study
• As clinically indicated.

If the baseline blood sample collection occurred within the previous 48 hours of cycle 1 day 1, the biochemistry does not need to be repeated at that time.

In the event of >Grade 2 non-hematological toxicities that require study treatment dose modifications or interruptions, hematological tests should be repeated until recovery to the baseline value or ≤ Grade 2. Refer to Table 3 for PD-0332991 treatment adjustments.

- *Pregnancy and assessments of fertility*

All females of childbearing potential should complete a serum pregnancy test at baseline ≤ 21 days prior to administration of PD-0332991, and at Day 1 of each cycle. Serum blood for pregnancy testing will be sent to the local laboratory. Adequate contraception must be used while on study and for 24 weeks after the last dose on PD-0332991.

To be considered “of non-childbearing potential”, it is advised that postmenopausal women be amenorrheic for at least 12 months or have a serum FSH > 40 mIU/ml or be at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy.

In case of pregnancy while on the study, the patient must be discontinued from the study.

If the baseline pregnancy test occurred within the previous 48 hours of cycle 1 day 1, the test does not need to be repeated at that time.

Pregnancy should be recorded on the Pregnancy Notification Form (Appendix 6) and reported by the investigator to the Sponsor.

Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment of any pregnancy outcome.

Any SAE experienced during pregnancy must be reported on the SAE Notification Form (Appendix 5). The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

7.2.3.6 ***Cardiac assessments***

- *Electrocardiogram (ECG)*

A standard 12 lead ECG will be performed at the time points specified below.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG section of the CRF. Each ECG tracing should be labeled with the study number, patient initials, patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities noted on the screening ECG should be recorded on the Medical History CRF page.

Any clinically significant findings must be discussed with the Sponsor and the Coordinating Investigator prior to enrolling the patient in the study. Clinically significant abnormalities noted at any point during the study should be recorded on the AE CRF.

ECG will be performed at:

• Baseline ≤ 21 days prior to the first dose of PD-0332991
• Days 1 and 15 in cycle 1
• Day 1 in subsequent cycles
• End of study
• Then as clinically indicated.

7.2.4 ***Biomarkers (optional)***

Fresh tumor biopsies FFPE (Formalin-Fixed Paraffin-Embedded) at screening and at Day 21 of Cycle 1 are encouraged to be collected. Once collected, the samples may be profiled by IHC, and array gene expression analysis to identify the pharmacodynamics activity of PD-0332991 in GIST patients.

As this is an active area of research, several biomarkers may be analyzed if justified by results of internal or external research activities.

Each site will send samples to Bergonie Institute with “Optional Pathology Request Form” (Appendix 10) completed for each sample.
All samples will be stored before they are analyzed.
The sample collection information must be captured on the appropriate CRF page(s)

All Pathological specimens sampling with documents must be sent to:

Institut Bergonié-Service Pathologie-
Technicienne Anapath Recherche Clinique
Protocole CYCLIGIST
229 cours de l’Argonne-33076 Bordeaux Cedex, France
Tél: 05.56.33.78.53

8. Criteria for stopping the treatment

Treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse events(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

Patients will be followed for 4 weeks after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

9. Criteria for stopping the trial

The trial can be suspended or stopped by the promoter (Institut Bergonié), in accordance with the coordinator, or upon request of the Competent Authority (ANSM) and/or the Ethics committee (Comité de Protection des Personnes), for the following reasons :

- an unexpected frequency and/or severity of the toxicity,
- an insufficient patient recruitment rate,
- A poor quality of the data collection.

10. Safety evaluation

10.1 Description of safety evaluation parameters

The safety evaluation will comprise an evaluation of the patient's general condition (ECOG Appendix 1), a physical exam, regular blood tests and the recording of adverse events occurring throughout the study. Toxicity will be evaluated using the CTCAE version 4 (Appendix 2).

In an emergency situation, the patient, his/her friends/family or treating physician will contact the investigator to report an event and/or to discuss the treatments to be implemented.

10.2 Methods and schedule to measure, collect and analyze the safety evaluation parameters

Patients will be seen for consultation every four weeks over the study period (every two weeks during the first cycle).

Blood tests are also planned every 2 to 4 weeks.

10.2.1 *Definitions*

10.2.1.1 Adverse event

An adverse event is defined as any untoward medical occurrence which occurs in a patient, a clinical investigation subject. Adverse events include, but are not limited to:

- abnormal test findings,
- clinical symptoms and signs,
- changes in physical examination findings,
- hypersensitivity,
- progression/worsening of underlying disease,

- lack of efficacy (for clinical trials, refer to the protocol),
- drug abuse,
- drug dependency
- death,
- hospitalization.
- any suspected transmission of an infectious agent via a Pfizer product.

As well as signs and symptoms resulting from:
- drug overdose,
- drug withdrawal,
- drug misuse,
- off-label use
- drug interactions,
- extravasation,
- exposure during pregnancy,
- exposure during breastfeeding,
- medication error,
- occupational exposure.

*10.2.1.2 **Serious adverse event***

A serious adverse event is defined as an adverse event regardless of the dose and that:
- results in death and/or,
- is life-threatening and/or,
- requires inpatient hospitalization or prolongation of existing hospitalization and/or,
- results in persistent or significant disability/incapacity and/or,
- results n congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is assessed as a serious adverse event with the seriousness criterion important medical event. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms “suspected transmission” and “transmission” are considered synonymous.

Whether or not corresponding to the above-mentioned criteria, any other adverse event considered as serious by any Pfizer agent, any healthcare professional or any investigator should be handled as a serious adverse event.

10.2.1.3 **Not serious adverse event**

- A non-serious adverse event is an adverse event whose characteristics do not meet the criteria of a serious adverse event.

10.2.1.4 **Adverse effect**

- An adverse effect is any untoward and unintended responses to an experimental drug regardless of the dose.

10.2.1.5 ***Expected/unexpected character :***

- An unexpected adverse event is an event whose nature, severity/intensity or outcome does not correspond to the information shown within the reference document for the study.
In practice, the term “new effect” is sometimes used as a synonymous of “unexpected adverse effect.

10.2.1.6 ***Special Considerations***

Certain product safety monitoring reports should be forwarded even if there is no associated adverse event. These reports involve circumstances that may increase the patient/consumer’s risk of developing adverse events.
These circumstances include:

- Lack of efficacy,
- medication errors,
- off-label use,
- exposure during pregnancy,
- exposure during breastfeeding,
- overdose,
- misuse,
- extravasation,
- occupational exposure

Some of these special circumstances are considered in more details below.

✓ Lack of efficacy: it is a failure to demonstrate pharmacological or therapeutic expected benefit.

✓ Medications errors: a medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.
A medication error does not necessarily involve the administration of the product (e.g. the error may have been corrected prior to administration of the product).

Potential medication errors or “near-misses,” which are individual reports of information or complaints about product name, labeling, or packaging similarities that do not involve a patient, are also reportable.

✓ Exposure during pregnancy: exposure during pregnancy refers to pregnancies where the fetus (from pre-embryo to birth) may have been exposed at a given time during pregnancy to a product from the Pfizer group (or a blinded treatment). Even if

there is no associated adverse event, exposure during pregnancy must always be reported. It can indeed provide the opportunity to obtain pregnancy outcome important information where appropriate.
Exposure during pregnancy may occur either:

- Through maternal exposure

a female becomes, or is found to be, pregnant either:

- while receiving a medicinal product
- after discontinuing a medicinal product
- during or following environmental exposure to a product from the Pfizer group (eg, a nurse reports she is pregnant and that she was exposed to chemotherapy drugs via inhalation or after accidentally overturning a bottle)

or

-Through paternal exposure

a male has been exposed to a medicinal product (either due to treatment or environmental circumstances) prior to or around the time of conception and/or is exposed during the partner pregnancy.

✓ Exposure during breastfeeding: exposure during breastfeeding occurs where an infant or child may have been exposed through breast milk to a medicinal product from the Pfizer group during breastfeeding by a female taking the product from the Pfizer group.

All drug exposure during breastfeeding cases are reported, whether or not there is an associated adverse event

Hospitalization or surgery planned before the patient's entry into the study does not be related as an SAE. Hospitalization for observation without associated adverse events should not be transmitted.

10.2.2 Serious adverse events and new information notification (responsibility of the investigator)

The investigator will notify the Vigilance Unit without delay about any serious adverse events or new events occurring:

- From the date of the informed consent is signed,
- During the whole patient follow-up period as defined by the research,
- Until 30 days after the end of patient follow-up period as defined by the research, if the event is likely to be research-related.

Type of Event	Reporting procedure	Deadline for reporting to the sponsor
SAE	SAE report form + written form if necessary	To be reported immediately to the sponsor
New information	Written report form	To be reported immediately to the sponsor
Pregnancy	Written report form	As soon as pregnancy is confirmed

The investigator must complete the “Serious Adverse Event Reporting Form” (Appendix 5) immediately, in English, and assess the relationship with the study

treatment. The form must then be dated, signed and sent by fax to the following address without delay to:

CELLULE DE VIGILANCE (VIGILANCE UNIT) - Unicancer
Fax: + 33 1 44 23 55 70
Or Contact: R&D Unicancer – E-mail: pv-R&D@unicancer.fr

For each event, the investigator will record:

- A description of the event that is as clearly as possible, using medical terminology,
- The date the event started and ended,
- The patient's relevant medical history,
- The steps taken and whether or not corrective treatment was required, whether or not the investigational treatment was discontinued, etc.
- Concomitant medications / therapies

The CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE Appendix 2) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP website at http://ctep.info.nih.gov/reporting/ctc.html. All appropriate treatment areas should have access to a copy of the CTCAE version 4.

- The causal link between this event and the trial treatment, disease treated or an intercurrent disease or treatment, or any obligation imposed by the research (a treatment-free period, additional examinations requested as part of the research etc.),
- Clinical course. If the event was not fatal, it should be monitored until recovery, until the patient has returned to his/her previous condition, or until any sequelae have stabilized,
- Whenever possible, the investigator must also attach the following with the serious adverse event report:
  - A copy of the hospitalization or extended hospitalization report,
  - A copy of the autopsy report, if required,
  - A copy of all the results of any additional tests performed, including relevant negative results, along with the normal laboratory values,
  - Any other document he or she considers useful and relevant.

All these documents must be anonymized. Additional information may be requested (by fax, by telephone or during a visit) by the CRA and/or by the Vigilance Unit using the Data Query form.

The investigator is responsible for providing appropriate medical follow-up for patients until resolution or stabilization of the adverse event or until the patient's death. Sometimes this may mean that follow-up will extend beyond the patient's withdrawal from the trial.

The investigator keeps the documents about the presumed adverse effect so that the information previously sent can be added to if necessary.

The investigator responds to requests for additional information from the Vigilance Unit in order to document the original observation.

10.2.3 *Non serious adverse events*

TYPE OF EVENT	REPORTING PROCEDURES	DEADLINE FOR REPORTING TO THE SPONSOR
Non-serious AE	Case report/record form	Does not need to be reported immediately

Non-serious adverse events will be reported by the investigator in the patient's CRF and will be followed up until complete resolution. The CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE Appendix 2) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.

If an adverse event becomes serious, it should be reported and followed-up as mentioned in the previous reporting procedures.

If the investigator would like to decrease trial treatment dose or temporarily stop study management without respecting protocol procedures, he/she should have previously discussed with the coordinator.

However, symptomatic treatment can be prescribed to manage the adverse event.

Any definitive interruption of the procedure has to be immediately notified to the sponsor. The patient remains in the study and is followed-up according to the procedures described in the protocol.

10.2.4 *Pharmacovigilance Unit*

The Vigilance Unit will analyze each SAE to define:

- Severity grading,
- Degree of relationship with study treatment,
- Whether expected or unexpected according the characteristics of study drug.

10.2.5 **Serious adverse events and new information notification (responsibility of the sponsor)**

10.2.5.1 SAE documentation

Sponsor undertakes to obtain from the investigators they report him immediately SAEs as defined above

10.2.5.2 Terms and SAEs transmission delays to Pfizer

SAEs must be notified to Pfizer, even if the information is incomplete, then the following information will be brought to sponsor's attention:

- **An identifiable patient:** notification must contain enough information on the involvement of a specific individual or a known number of specific individuals. A patient or a defined number of patients are considered identifiable if at least one of the following characteristics is known: sex, age, age group, date of birth, initials, or identification number the patient (in case of clinical trials) is available.

- **A suspect product:** notification shall appoint (or clearly refer to) a product of Pfizer.

- **A serious adverse event:** notification must contain at least a description of SAE such as signs and symptoms, diagnosis, or circumstances involving a risk event with or without associated adverse events, such as exposure during pregnancy, exposure during lactation, overdose, misuse, medication error and extravasation.

- **An identifiable notifier:** notifier must be identifiable and have had direct contact with the identifiable patient (that is to say that the notification is not based on a rumor). Notifier is considered identifiable if at least one of the following is available: name or initials, address or qualification (eg GP, dentist, pharmacist).

In cases of pregnancy, the notification must include the expected date of delivery. The subject will be followed until the end of pregnancy and Pfizer will be notified via a supplementary report to the outcome of pregnancy.

- *Particular condition: medication error*

If there has been no administration of product, medication error should be reported when existing an identifiable notifier, a suspect product and a proven medication error or medication error risk;
When there is involvement of a patient, we need the three criteria described above, and the patient must be identifiable to report the case.

Case of lack of efficacy:
Cases of lack of efficacy must be reported if they are associated with an SAE.

Only disease progression resulting in death must be transmitted. Progression of the disease leading to hospitalization should not be reported.

The Promoter shall transmit to the pharmacovigilence department of Pfizer, regardless of causality, all SAEs occurring over a defined period in a subject receiving the product object of research within 24 hours after taking knowledge of the event. Transmission of deaths or life-threatening event must be immediate upon taking knowledge.

For SAEs transmission to Pfizer, sponsor will use the SAE declaration form of UNICANCER and the declaration of pregnancy of UNICANCER, accompanied by a letter indicating the number of transmitted pages, complete coordinates of sender, name of research, the sequence of report (initial or supplementary report), and if it is a death or a life-threatening event. Transmission occurs preferentially by fax.

*10.2.5.3 **Recipient of declarations***

The coordinates of Pharmacovigilance notification recipients are:
PFIZER – Département Pharmacovigilance
Téléphone: 01 58 07 33 89 / 0800 39 84 50
Fax: 01 70 74 57 33

Transmission occurs preferentially by fax.

*10.2.5.4 **Reporting period of SAEs***

SAEs subject to these reporting obligations to Pfizer are SAEs occurring between the first dose of a Pfizer product up to twenty-eight (28) days after the last dose of the Pfizer product. The end of the period may be extended after twenty-eight (28) days depending on product characteristics (eg, long half-life) or in terms of safety profile, this extension is specified in the protocol. End of this period can't be less than twenty-eight (28) days after the last administration.
All SAEs considered related will be reported regardless of the time of onset (during or after the end of the study).

10.2.5.5 SAEs monitoring and complementary informations

Sponsor undertakes to obtain from the principal investigators that they provide him all complementary information in the same way as the initial information. The pharmacovigilance department of Pfizer may need reasonably contact with the Promoter for monitoring SAE. Additional information will be provided on the same terms and the same time that the initial information.

10.2.5.6 Competent authorities SAEs reporting

SAEs' Pfizer transmission doesn't absolve sponsor to declare them to ANSM and CPP, and competent authorities of other countries in which research takes place, possibly in the context of its obligations as Sponsor .

10.2.5.7 Use of data by Pfizer

Pfizer may freely use information about these SAEs under continuous evaluation of the benefit / risk ratio.

10.2.6 Notification and registration of unexpected serious adverse events and new information (Responsibility of the sponsor)

The sponsor notifies unexpected serious adverse events and new information to the Regulatory Authorities (in person, or through an organization which has received allowances for this task) according to the usual notification procedures

11. Evaluation criteria

11.1 Primary endpoint

Efficacy is assessed based on 4-month non progression. Non progression is defined as complete or partial response (CR, PR) or stable disease (SD), using the Response Evaluation Criteria in Solid Tumors (RECIST v1.1 Appendix 3). Non-progression rate will be calculated as the number of alive and progression free patients divided by the number of eligible and assessable patients for the efficacy analysis.

Eligible and assessable populations are described in section 12.2

As recommended by RECIST v1.1 (Appendix 3), all claimed response will be centrally reviewed by an expert of the study. The results of the centralized radiological review will be used for the analysis of the primary endpoint.

11.2 Secondary endpoints

- Objective response is defined as complete response (CR) or partial response (PR) according to RECIST v1.1 (Appendix 3).
- Progression-free survival is defined as the time from the first administration of treatment to progression (as per RECIST v1.1 Appendix 3) or death of any cause, whichever occurs first

- Overall survival is defined as the time from the first administration of treatment to death.
- Progression will also be assessed using CHOI criteria (Appendix 4)
- Safety of PD-0332991 will be assessed by the Common Terminology Criteria for Adverse Events (CTCAE), v4.0 (Appendix 2).

12. Statistical considerations

12.1 Sample size calculation

The primary evaluation endpoint is the non-progression rate at 4 months.

- We rely on an optimal two-stage Simon's design (Simon, 1989). Based on the following hypotheses under PD-0332991 treatment:

- 25% non-progression rate (null hypothesis),
- 45% acceptable non-progression rate (alternative hypothesis),
- 5% type I error rate,
- 90% power,

A total of 57 assessable subjects will be necessary, with 22 assessable subjects recruited to the first stage.

- Stage 1: Following the inclusion of the first 22 assessable patients, if 6 or less patients are progression-free (complete response, partial response or stable disease), the study will be terminated early. Otherwise, the second group of 35 subjects will be recruited.
- Stage 2: If at the end of recruitment, 20 patients or more are progression-free (out of the 57 evaluable patients), PD-0332991 will be considered worthy of further testing in this disease.

Eligible and assessable populations are described in section 12.2

Given the disease is rare and the absence of standard treatment in this indication, inclusion will not be suspended after the recruitment of the first 22 patients. Inclusion will be pursued, while data on the first 22 patients will be analyzed.

In order to account for not evaluable patients (+/- 10%), **63 patients** will be recruited.

The anticipated accrual rate is 3-4 patients/months.

12.2 Study populations

Eligible population: All patients included without major violation of eligibility criteria.

Population evaluable for efficacy: All patients eligible and for whom the following conditions are satisfied:

- Received at least one complete or two incomplete treatment cycles,
- At least one disease measurement recorded not less than four weeks after treatment onset.
- Diagnosis of GIST established either by (i) a center of the RREPS network, or (ii) Pr JM Coindre or collaborators.

The following patients will also be included in the population evaluable for efficacy; they will be considered as failures for the primary endpoint (i.e. disease progression at four months) and not be replaced in the primary efficacy analysis:

- Any eligible patients who received at least one treatment cycle or two incomplete and experienced disease progression or died due to disease progression prior to any radiological evaluation (will be considered as an “early progression”).
- Patients who study-drug treatment definitively stopped due to toxicity of PD-0332991, without any tumor assessments after the start of study treatment.
- Patients who received at least one administration of PD-0332991 and study-drug treatment definitively stopped due to significant clinical deterioration of unknown reason and without any tumor assessments after the start of study treatment.

For a definition of patients' replacement, see section 5.6.

Safety population: all patients having received at least one administration of PD-0332991.

12.3 Statistical analysis

The patients entered into the study will be described according to the following characteristics:

- Compliance with eligibility criteria,
- Epidemiological characteristics,
- Clinical and laboratory characteristics,
- Treatment characteristics.

12.4 Endpoint analysis

- The primary efficacy endpoint will be analyzed at 4 months based on the population assessable for the primary endpoint (see chapter 11.1 for definition).
- As regards the other efficacy endpoints, the analyses will be carried out in the assessable population.
- The safety analysis will be performed on the safety population.
- Quantitative variables will be described using mean and standard errors if the normality assumption is satisfied, else other descriptive statistics (median, range, quartiles) will be used.
- Qualitative variables will be described using frequency, percentage and 95% confidence interval (binomial law).
- Survival endpoints will be analyzed using the Kaplan-Meier method. The median survival rates will be reported with a 95% confidence interval. Median follow-up will be calculated using the reverse Kaplan-Meier method. Multivariate analyses can also be carried out based on Cox’s proportional risk method and after checking the risk proportionality hypothesis.

12.5 Interim statistical analysis

An interim statistical analysis will be carried out after the inclusion of the first 22 eligible and assessable patients. The trial will be terminated if 6 or less patients are progression-free (complete response, partial response or stable disease). Otherwise, the second group of 35 subjects will be recruited. A statistical report will be produced by the statistician of the study. Inclusion will not be suspended during this interim analysis.

13. Quality Insurance and Trial Monitoring

13.1 Monitoring of the trial

13.1.1 *Steering Committee*

The study will be supervised and monitored by a Steering Committee comprising members participating in the study:

- Dr A. Italiano, Co-ordinating Investigator and Chairman of the Commitee,
- Dr BN. Bui, Investigator and medical oncologist,
- Pr S. Mathoulin-Pélissier, Head of the Clinical Research and Epidemiology Unit,
- C. Bellera, Biostatistician,
- Dr B. Lortal, Pharmacist
- D. Juzanx, Coordinating Clinical research assistant

This committee must ensure the following:

- Implementation and regular follow-up of the study
- Patient protection,
- That the trial is conducted ethically, in accordance with the protocol,
- That the trial benefit/risk ratio is evaluated and the scientific results are checked during or at the end of the trial.

It decides on any relevant amendment to the protocol that is required in order to continue the trial (protocol amendments prior to submission to the EC and the relevant Health Authorities, decisions on whether to open or close research sites, discussion of results and the strategy for the publication of these results). It must inform the sponsor of any decisions taken. Decisions concerning a major amendment or a change to the budget must be approved by the sponsor.

13.1.2 *Independent Data Monitoring Committee*

An independent Data Monitoring Committee (IDMC) will be created at the request of the relevant Authority, the sponsor or the Steering Committee. The IDMC plays an advisory role for the Sponsor, who has the final decision regarding the implementation of recommendations put forward by the IDMC.

Composition of the IDMC

- This Committee must comprise one qualified oncologist, one pharmacologist and one statistician :
  - Qualified oncologist (Dr Sophie Piperno Neumann)
  - Pharmacologist (Dr Driss Berdaï)
  - Statistician (Mrs Sophie Gourgou)

All of whom will have experience in the monitoring and analysis of clinical trials. One of these members will be appointed as the Trial Rapporteur.

- Each of these members must be unconnected with the trial and cannot, therefore, belong to a centre of the trial.
- These members are appointed by the Sponsor in consultation with the trial co-ordinator and the Steering Committee.

Responsibilities of the IDMC

The IDMC is responsible for the following:

- Analysing preliminary efficacy and safety data,
- Making recommendations on the continuation, early discontinuation (in the case of toxicity or lack of efficacy) or publication of the trial results,
- Drafting the minutes after each meeting and monitoring their confidentiality.

Any recommendation from the IDMC that can be made public will be announced by the Sponsor and not by the Steering Committee. The Sponsor is responsible for sending IDMC recommendations to the regulatory authorities [ANSM (French Agency for the Safety of Health Care Products) and EMEA (European Medicines Evaluation Agency)].

13.2 Quality assurance

13.2.1 Data collection

The data will be collected on an electronic case report form and directly input via the Internet. Only the investigators and the Investigator's Clinical Research Assistants (CRAs) appointed by the later and duly authorized by the sponsor will be authorized to enter the data.

Data will be handled by online trial management software on the Internet (Macro v4, Infermed Company); it will be transferred and monitored remotely in real time.

The study CRA and/or any other person appointed by the sponsor will be available to assist the investigators in carrying out the study and to ensure that the trial is carried out in accordance with the protocol.

The study CRA will contact the investigators regarding the study implementation visit.

All the study-related documents will be available on the Internet site: protocol, pre-selection form, randomization form, informed consent form, serious and non-serious adverse event report form, centralized tube dispatch form, etc.

All of the necessary data will be collected on an electronic case report form provided by the sponsor. The generic names of the concomitant medication will be given in French.

Corrections made to the original data must be justified. These corrections will be automatically dated and signed by the authorized member of staff via the personalized password allocated at the start of the study.

The case report form will be validated by the investigator or the CRA at the authorized center whenever data is entered.

Laboratory data exceeding normal limit values will be commented upon if they are considered clinically significant. Data other than that requested within the scope of the protocol can be collected as additional data; their interest will be specified.

13.2.2 Monitoring

In order to guarantee the authenticity and credibility of the data in accordance with the principles of GCP (Good Clinical Practice) dated 24 November 2006, the sponsor shall implement a quality assurance system comprising:

- the management and monitoring of the trial in accordance with the procedures stipulated by the Institut Bergonié,
- the quality control of the research site data by the CRA whose role is to:

- check compliance with the protocol, GCP and current legislation and regulations,
- check the consent and eligibility of each patient taking part in the trial,
- check the consistency and coherence of case report form date against the source documents.
- check that each serious adverse event is reported,
- monitor the traceability of the study medication (dispensation, storage and drug accountability),
- check, where applicable, that the persons likely to take part in the trial are not already participating in another trial that could prevent them from being included in the clinical trial proposed. The CRA shall also ensure that the patients have not participated in a trial for which an exclusion period currently applies.

- The possible audit of study centers
- The centralized review of certain protocol criteria.

The check procedures will include:

- Study progression,
- Protocol compliance,
- The updating of information on the Internet site.

The checking of data by comparing the information on the electronic case report form and the original clinical or laboratory data is one of the monitoring procedures.

The following will be checked, in particular, for each patient (100% level): patient identification, informed consent (procedure and signature), selection criteria, therapeutic procedure, adverse events, principal response variables. The personal data relating to each patient shall remain confidential. On the electronic case report form or any other form dispatched, the patients will be identified solely by their initials (2/name – 2/surname) and an inclusion number. However, the investigators must keep a list identifying the patients in their folders.

The CRAs responsible for the quality control of this clinical trial are duly appointed by the sponsor for this particular purpose and must have access, with the consent of those involved, to individual trial participant data required strictly in accordance with this control procedure. The CRAs are subject to professional secrecy under the conditions defined by Articles 226-13 and 226-14 of the French penal code. The traceability of monitoring visits is guaranteed by a written monitoring report.

The investigators shall undertake to give CRAs direct access to the medical records of each patient in order to allow the CRAs to ensure optimal quality control of the trial. The same applies to health authority representatives.

13.2.3 *Handling of missing data*

The monitoring of data for adverse events will be carried out regularly in order to effectively limit the amount of missing data likely to prevent or hamper trial implementation and analysis.

13.2.4 Audits

The sponsor, the local authorities or the authorities to which information about this study has been submitted can decide to have an audit. All the documents relating to this study must be available for such an inspection after prior notification.

14. Ethical, legislative and regulatory considerations

Clinical Research Management Unit – Institut Bergonié
Contacts: Pauline Beaufrere – Tel.: +33 5 56 33 32 70 – e-mail:
p.beaufrere@bordeaux.unicancer.fr
or Marie-Laure Marty – Tel.: +33 5 47 30 60 79 – e-mail:
m.marty@bordeaux.unicancer.fr

The study will be carried out in accordance with:

- The ethical principles of the current version of the "Declaration of Helsinki"
- Good Clinical Practice (GCP): I.C.H. version 4 of 1 May 1996 and decision dated 24 November 2006 (Official Bulletin of 30 November 2006, text 64).
- European Directive (2001/20/EC) on clinical trial procedures.
- Huriet's law (No. 88-1138) dated 20 December 1988, concerning the protection of persons taking part in Biomedical Research with the provisions of the Public Health law (No. 2004-806) of 9 August 2004 and implementation decree No. 2006-477 of 26 April 2006 relating to biomedical research.
- The French law on Data Protection and Civil Liberties, No. 78-17 of 6 January 1978 modified by law No. 2004-801, dated 6 August 2004, concerning the protection of persons with regards to the processing of personal data.
- The application of Circular DHOS/INCA/MOPRC/2006/475 of 7 November 2006: the Sponsor shall undertake to register the Trial and thus make it accessible to the general public, in the INCa (French Cancer Institute) register via the Internet site: www.e-cancer.fr. Each trial published in the INCa register will be sent to the NCI for registering on the following site: www.clinicaltrials.gov. The trial will be registered before the first patient is entered into the study. The Sponsor is responsible for updating the study data in order to guarantee the reliability of the information available on-line.
- Law no. 2004-800 dated 6 August 2004, concerning bioethics amended by law No. 2012-387, dated 22 March 2012.

14.1 Clinical trial authorization

This trial is registered under Eudract N° 2013-000283-28

The protocol has been approved by the South West and Overseas Territories III Ethics Committee, Bordeaux. Approval was given on 30/10/2013.

The Relevant Authority, the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM - French Agency for the Safety of Health Care Products) authorized the clinical trial on 13/11/2013.

Any amendments to the protocol concerning study objectives, patient population and principal methods will require an amendment, which must be approved by the EC

and l'ANSM. The sponsor will inform the EC and ANSM of expected and/or unexpected serious adverse events in accordance with current regulations.

The sponsor will send the summary of the final report to the relevant Authority within one year of completion of the trial.

14.2 Insurance policy

The Institut Bergonié has taken out an insurance policy (policy No.0100871914011-130002-10998) with the HDI GERLING France Company, TOUR OPUS 12, 77, Esplanade de la Défense 92914 Paris LA DEFENSE through an insurance broker, namely Biomédic Insure (Parc d'Innovation Bretagne Sud, CP 142, 56038 Vannes, tel. 02 97 69 19 19) in case compensation is payable to investigators or patients taking part in the study.

14.3 Informing and obtaining consent from patients

The investigator in charge of the patient will provide the latter with relevant information relating to the study objectives, potential benefits and possible adverse events. The study methods will be outlined. The patient can refuse treatment before or at any time during the study, without experiencing any adverse repercussions in terms of his/her subsequent care.

The patient's written consent will be informed prior to entry into the study. Three copies will be available: one for the patient, the second for the investigator and the third for the sponsor. This written consent form will be kept for 15 years by the investigator.

The Patient Information Leaflet and Informed Consent Form must be combined in the same document in order to ensure that all of the information is given to the trial participant.

The consent form must be personally dated and signed by the trial participant and the investigator. The participant must also initial all of the pages in the Patient Information Leaflet. The original will be archived in the investigator's folder and the duplicate will be sent to the trial participant.

14.4 Sponsor's responsibilities

The sponsor of the clinical trial, the Institut Bergonié, will take the initiative for this clinical trial. The Institute will manage the trial and ensure that finance is provided.

The sponsor's main responsibilities are to:

- Take out civil liability insurance,
- Obtain the Eudract No. and register the trial in the European database (European Drug Regulatory Authorities Clinical Trials),
- Obtain clinical trial authorization for the initial project and any amendments from the DC and ANSM; approval by the EC and decision taken by ANSM.
- give trial-related information to the site directors, pharmacists and investigators,
- notify the relevant authority of the trial start and end dates,
- draft the final trial report and sent the summary to ANSM,
- send to Pfizer all SAEs collected from the clinical trial,
- send the trial results to the relevant authority, EC and trial participants,

- Archive essential trial documents in the sponsor's folder for a minimum period of 15 years after the trial has ended.

14.5 Investigator's responsabilities

The senior investigator of each establishment concerned undertakes to conduct the clinical trial in accordance with the protocol that was approved by the ethics committee and the relevant authority (ANSM).

The investigator must not make any changes to the protocol without the written consent of the sponsor or without the ethics committee and the relevant authority having authorized the proposed changes.

It is the responsibility of the senior investigator is:

- to provide the sponsor with his/her curriculum vitae as well as those of his/her co-investigators,
- to identify the members of his/her team who are participating in the trial and to define their responsibilities,
- to start patient recruitment after authorization has been obtained from the sponsor,
- to ensure that he/she is available for "monitoring" purposes and for investigators' meetings.

It is the responsibility of each investigator:

- to comply with the confidential nature of the trial,
- to obtain informed consent, signed and dated personally by each trial participant, before any screening procedures specific to the trial are carried out,
- to regularly complete the case report forms (CRFs) for each of the patients enrolled in the trial and to allow the Clinical Research Assistant (CRA) direct access to source documents so that the latter can validate the data on the CRF,
- to promptly notify Unicancer of any serious adverse event and/or new information occurring during the trial,
- to date, correct and validate corrections on the case report forms (CRFs) and the Data Query Forms (DQFs).

14.6 Authority to execute the trial

The investigator shall certify that he/she is authorized to enter into this agreement and that the terms and conditions of the protocol and agreement do not conflict with other work contracts that the investigator may have entered into with any other party, or any other arrangement agreed by the Institution where the investigator is employed.

14.7 Regulations governing the collection of human biological samples

During the medical procedures to be carried out, samples will be collected for medical purposes. A fraction of these samples will be kept and used for scientific research purposes.

The patient will be informed of this research and provided that he/she approves by signing an informed consent, these samples intended for research will be:

- Initially prepared and stored using a specific technique to preserve them under excellent conditions.
- and secondly, used within the scope of this research.

The preparation, storage and use of these samples will not in any way affect current or future medical care administered to the patient for the purpose of diagnosis or treatment.

The results of this research may, in future, appear in scientific publications. All of the data shall remain anonymous.

Obtaining and using additional samples

This biomarker study is made up of exploratory research that is described in the section “Ancillary Study”.

On completion of the trial, provided that the patient agrees and provided that not all of the samples have been used, the said samples can be used for subsequent scientific research purposes without the approval of the Ethics Committee (EC) and the signing of a new consent form by the patients included.

14.8 Federation des comités de patients pour la recherche clinique en cancerologie (FCPRCC) (Federation of patient commitees for clinical research in oncology)

The Fédération des Comités de Patients pour la Recherche Clinique en Cancérologie (FCPRCC) (Federation of Patient COmmittees for Clinical Research in Oncology) was created on the initiative of the Fédération des Centers de Lutte Contre le Cancer (FNCLCC) (Federation of Anti-Cancer Centers) and the Ligue Nationale Contre le Cancer (National Anti-Cancer League) in order to review clinical trial protocols in oncology. This Federation of Patient Committees is co-ordinated by the Office for Clinical and Therapeutic Trials and groups together the League patient committees as well as other health care establishments. It undertakes to review the protocol and to propose improvements focusing primarily on the quality of the information leaflet, the availability of a treatment and monitoring plan and the suggestion of measures aimed at improving patient comfort.

14.9 Data processing

In accordance with the revision of the French Data Protection and Liberties Act of 06 August 2004 and its implementation decree, the Sponsor shall follow the methodology of reference MR001 of the Commission Nationale de l’Informatique et des Libertés (French National Commission for Data Protection and Liberties).

Furthermore, if the biomedical research data is computer processed or managed by computerized systems, each Center:

- shall check and document the fact that the computerized systems used in the research comply with requirements drawn up in relation to data integrity, accuracy and reliability, as well as compliance with expected performances (i.e. validation);
- shall implement and ensure the monitoring of standard operating procedures relating to the use of these systems;

- shall ensure that the design of these systems allows for data to be amended such that the amendments are documented and that any item of data input cannot be deleted (i.e. maintaining data and amendment audit trail) ;
- shall implement and ensure the monitoring of a secure system that prevents any unauthorized data access;
- shall update the list of persons authorized to amend the data;
- shall keep appropriate back-up copies of the data;
- shall maintain blind status, where applicable (e.g. during data entry and processing);
- shall ensure that personal data used within the scope of the trial is processed in accordance with the conditions defined by law No. 78-17 dated 6 January 1978 relating to data processing, files and liberties modified by law No. 2004-801 of 6 August 2004 and regulatory texts applicable to its application.

If the data is converted during processing, it must always be possible to compare the original data and observations with the data after conversion.

The system used to identify subjects taking part in the trial must not present with any ambiguity and must allow all of the data collected for each of these subjects to be identified whilst maintaining the confidentiality of the personal data, in accordance with law No. 78-17, duly amended.

15. Confidentiality and ownership of data

All of the information communicated or obtained and the data and results generated by the trial legally belong to the Institut Bergonié, which can use this data at its own discretion. The trial cannot be the subject of any written or verbal comments without the sponsor's consent.

Any unpublished data sent to the investigator is confidential. These documents must not be disclosed to a third party without the consent of the Institut Bergonié. The submission of these documents to the EC is formally authorized. The Institut Bergonié is free to submit the trial data and results to governments and other accredited authorities.

The investigator must treat as confidential all of the information acquired or deduced during the trial and shall take the necessary steps to avoid any violation of this confidentiality, with the exception of information that must be disclosed in accordance with the legislation.

16. Regulations governing publication

16.1 Final report

The biostatistician(s) will compile a final report. It will include tables giving the raw data and the statistical report on the data. This report will be submitted to the Steering Committee and Senior Investigators for approval and signature. A report of the overall results of the study will be issued so that the investigator can send it to patients who wish to know these results.

16.2 Publications

All of the information arising from this study shall be considered confidential at least until the appropriate analysis and subsequent checks have been completed by the trial sponsor, co-ordinating investigator and statistician.

All forms of publication must be submitted to the Steering Committee for review and approval prior to publication (allowing at least 15 working days for abstracts and oral presentations, and 45 working days for written publications). The Steering Committee shall check the accuracy of the information submitted (in order to avoid any inconsistency with that submitted to the Health Authorities), and ensure that confidential information is not inadvertently disclosed. It will also provide additional information as required.

Furthermore, all memos, manuscripts or presentations must comprise a heading referring without fail to the Institut Bergonié, all of the institutions, investigations, co-operating groups and learned societies that have contributed to the implementation of the trial, and listing any organizations that have provided financial support.

For the principal publication, either in French or English, the authors are:

- the study coordinator (first or last if an insufficient number of patients is recruited)
- the investigators will be listed on a pro rata basis according to the number of patients recruited, regardless of the co-operating group. Each investigator site shall allocate a member of staff who will act as author for official presentations/publications.
- a representative of each co-operating group not listed amongst the study centers having the largest patient cohorts
- a representative of the trial statistics unit (in the first 3 positions according to degree of involvement in the preparation of publications)

As required for multicenter studies, the first publication will present the data collected in all of the participating centers after the information has been analyzed in accordance with the protocol by a biostatistician, and not by the investigators.

Similarly, publications of additional results (laboratory study) shall include the name of the person who carried out the additional work as well as the names of all the other persons involved in this additional work.

Correspondents in the recruitment centers with lower patient cohorts not cited in the main publication should ideally be included in subsequent publications.

Unless granted special authorization by the Steering Committee, the investigators cannot publish the results collected in only one or two centers before the first official version, containing all of the data, is published.

17. References

Angevin E, Grünwald V, Lin C et al (2010) A Phase I/II Study of Dovitinib (TKI258), an FGFR and VEGFR Inhibitor, in Patients With Advanced or Metastatic Renal Cell Cancer (mRCC): Preliminary Phase II Ann Oncol, 21: Abstract 507P

Assamaki R, Sarlomo-Rikala M, Lopez-Guerrero JA, et al. (2007) Array comparative genomic hybridization analysis of chromosomal imbalances and their target genes in gastrointestinal stromal tumors. Genes Chromosomes Cancer 46:564–76.

Astolfi A, Nannini M, Pantaleo MA, et al. (2010) A molecular portrait of gastrointestinal stromal tumors: an integrative analysis of gene expression profiling and high-resolution genomic copy number. Lab Invest 90:1285–94.

Belinsky MG, Skorobogatko YV, Rink L, et al. (2009) High density DNA array analysis reveals distinct genomic profiles in a subset of gastrointestinal stromal tumors. Genes Chromosomes Cancer 48:886–96.

Bovelli D, Plataniotis G, Roila F (2010) Cardiotoxicity of chemotherapeutic agents and radiotherapy-related heart disease: ESMO Clinical Practice Guidelines. Ann Oncol Volume 21 Supplement 5: 277-282.

Buchdunger E, Zimmermann J, Mett H, et al (1996) Inhibition of the Abl protein-tyrosine kinase in vitro and in vivo by a 2-phenylaminopyrimidine derivative. Cancer Res; 56: 100-104.

Casali, P. G, Blay, J. Y (2010) on behalf of the ESMO/ CONTICANET/ EUROBONET Consensus Panel of Experts. Gastrointestinal stromal tumours: ESMO clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncol (supplement 5): v98-v102.

Chibon F, Lagarde P, Salas S, et al. (2010) Validated prediction of clinical outcome in sarcomas and multiple types of cancer on the basis of a gene expression signature related to genome complexity. Nat Med 16:781–7.

Choi H, Charnsangavej C, Faria SC, et al (2007) Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of a new computed tomography response criteria. J Clin Oncol; 25: 1753-1759.

Corless CL, Fletcher JA, Heinrich MC (2004) Biology of gastrointestinal stromal tumors. J Clin Oncol; 22: 3813-3825.

Dagher GD, Cohen M, Williams G, et al (2002) Approval summary: imatinib mesylate in the treatment of metastatic and/or unrespectable malignant gastrointestinal stromal tumors. Clin Cancer Res; 8: 3034-3038.

De Giorgi U, Verweij J (2005) Imatinib and gastrointestinal stromal tumors: Where do we go from here?. Mol Cancer Ther; 4: 495-501.

DeMatteo RP, Lewis JJ, Leung D, et al (2000) Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors fro survival. Ann Surg; 231: 51-58.
Demetri GD, van Oosterom AT, Garrett CR, et al (2006) Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomized controlled trial. Lancet; 368: 1329-1338.

Demetri GD, von Mehren M, Blanke CD, et al (2002) Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med; 347: 472-480.

Demetri GD, Reichardt P, Kang YK et al. (2012) 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, In Press.

Eisenhauer EA, Therasse P, Bogaerts J et al (2009) New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). EJC; 45: 228-247

El-Rifai W, Sarlomo-Rikala M, Andersson LC, et al. (2000) DNA sequence copy number changes in gastrointestinal stromal tumors: tumor progression and prognostic significance. Cancer Res 60:3899–903.

Emory TS, Sobin LH, Lukes L, et al (1999) Prognosis of gastrointestinal smooth-muscle (stromal) tumors: dependence on anatomic site. Am J Surg Pathol; 23: 82-87.

Finn RS, Dering J, Conklin D et al. (2009) PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. Breast Cancer Res. 11:R77.

Fletcher CD, Berman JJ, Corless C, et al (2002) Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol; 33: 459-465.

Haller F, Lobke C, Ruschhaupt M, et al. (2008) Loss of 9p leads to p16INK4A down-regulation and enables RB/E2F1-dependent cell cycle promotion in gastrointestinal stromal tumours (GISTs). J Pathol 215:253–62.

Hamilton SR, Aaltonen LA (eds) (2000) World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Digestive System. Lyon: IARC Press.

Heinrich MC, Corless CL, Duensing A, et al (2003) PDGFRA activating mutations in gastrointestinal stromal tumors. Science; 299: 708-710.

Heinrich MC, Griffith DJ, Druker BJ, et al (2000) Inhibition of c-kit receptor tyrosine kinase activity be STI 571, a selective tyrosine kinase inhibitor. Blood; 96: 925-932

Hirota S, Isozaki K, Moriyama Y, et al (1998) Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science; 279: 577-580.

Hirota S, Ohashi A, Nishida T, et al (2003) Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. Gastroenterology; 125: 660-667.

Huang HY, Li SH, Yu SC, et al. (2009) Homozygous deletion of MTAP gene as a poor prognosticator in gastrointestinal stromal tumors. Clin Cancer Res 15:6963–72.

Katsumi Y, Iehara T, Miyachi M, et al. (2011) Sensitivity of malignant rhabdoid tumor cell lines to PD 0332991 is inversely correlated with p16 expression. Biochem Biophys Res Commun. 413:62-8.

Konecny GE, Winterhoff B, Kolarova T. et al. (2011) Expression of p16 and retinoblastoma determines response to CDK4/6 inhibition in ovarian cancer. Clin Cancer Res. 17:1591-602.

Italiano A, Cioffi A, Coco P et al. (2012) Patterns of care, prognosis, and survival in patients with metastatic gastrointestinal stromal tumors (GIST) refractory to first-line imatinib and second-line sunitinib. Ann Surg Oncol. 19:1551-9.

Joensuu H, Roberts PJ, Sarlomo-Rikala M, et al (2001) Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stomal tumor. N Engl J Med; 344: 1052-1056.

Kim NG, Kim JJ, Ahn JY, et al. (2000) Putative chromosomal deletions on 9P, 9Q and 22Q occur preferentially in malignant gastrointestinal stromal tumors. Int J Cancer 85:633–8.

Kindblom LG, Remotti HE, Aldenborg F, et al (1998) Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol; 152: 1259-1269.

Lagarde P, Pérot G, Kauffmann A. et al. (2012) Mitotic checkpoints and chromosome instability are strong predictors of clinical outcome in gastrointestinal stromal tumors. Clin Cancer Res. 18:826-38.

Marumoto T, Zhang D, Saya H. Aurora-A - a guardian of poles. (2005) Nat Rev Cancer 5:42–50.

Mazur MT, Clark HB (1983) Gastric stromal tumors: Reappraisal of histogenesis. Am J Surg Pathol; 7: 507-519.

Miettinen M, Majidi M, Lasota J (2002) Pathology and diagnostic criteria of gastrointestinal stromal tumors (GISTs): a review. Eur J Cancer; 38(Suppl 5): S39-51

National Institutes of Health (2009) Therapy Evaluation Program. Common Terminology Criteria for Adverse Events, v4.0. Available at the official NCI CTCAE site (http://evs.nci.nih.gov/ftp1/CTCAE/About.html)

Nilsson B, Bumming P, Meis-Kindblom JM, et al (2005) Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era- a population-based study in western Sweden. Cancer; 103: 821-829.

Perez-Atayde AR, Shamberger RC, Kozakewich HW (1993) Neuroectodermal differentiation of the gastrointestinal tumors in the Carney triad: An ultrasound and immunohistochemical study. Am J Surg Pathol; 17: 706-714.
Perrone F, Tamborini E, Dagrada GP, et al. (2005) 9p21 locus analysis in high-risk gastrointestinal stromal tumors characterized for c-kit and platelet-derived growth factor receptor alpha gene alterations. Cancer 104:159–69.

Plaat BE, Hollema H, Molenar WM, et al (2000) Soft tissue leiomyosarcomas and malignant gastrointestinal stromal tumors: differences in clinical outcome and expression of multidrug resistance proteins. J Clin Oncol; 18: 3211-3220.

Romeo S, biec-Rychter M, Van GM, et al. (2009) Cell cycle/apoptosis molecule expression correlates with imatinib response in patients with advanced gastrointestinal stromal tumors. Clin Cancer Res 15:4191–8.

Rousset D, Agnes F, Lachaume P, et al (1995) Molecular evolution of the genes encoding receptor tyrosine kinase with immunoglobulin-like domains. J Mol Evol; 41: 421-429.

Sarker D, Evans TRJ, Judson I et al (2010) CHIR-258: preliminary data from a first in human phase 1 dose escalating trial of an oral, selectively targeted receptor tyrosine kinase inhibitor in patients with solid tumors , World Health Organization (1979) WHO Handbook for Reporting Results of Cancer Treatment. Geneva: World Health Organization.

Schneider-Stock R, Boltze C, Lasota J, et al. (2003) High prognostic value of p16INK4 alterations in gastrointestinal stromal tumors. J Clin Oncol 2003;21:1688–97.

Schneider-Stock R, Boltze C, Lasota J, et al. (2005) Loss of p16 protein defines high-risk patients with gastrointestinal stromal tumors: a tissue microarray study. Clin Cancer Res 11:638–45.

Schvartzman JM, Sotillo R, Benezra R. (2010) Mitotic chromosomal instability and cancer: mouse modelling of the human disease. Nat Rev Cancer 10:102–15.

Simon R. (1989) Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 10:1-10.

Yarden Y, Kuang WJ, Yang-Feng T, et al (1987) Human proto-oncogene c-kit: a new cell surface receptor tyrosine kinase for an unidentified ligand. Embo J; 6: 3341-3351.

18. APPENDIX

APPENDIX 1: ECOG PERFORMANCE STATUS ASSESSMENT SCALE

Grade	Activity
0	Able to carry on all normal activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

APPENDIX 2: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) V4

TOXICITY EVALUATION CRITERIA The CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE)

You can download this document in PDF:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

APPENDIX 3: EVALUATION OF RESPONSE. THE RECIST V1.1

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

DEFINITIONS

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

DISEASE PARAMETERS

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

METHODS FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

RESPONSE CRITERIA

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Definition of the Best Response

The best response determination in trial where confirmation of complete or partial response is required:

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (**generally 4 weeks later**). In this circumstance, the best overall response can be interpreted as in Table below.

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR (complete response) may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic detioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is *not* a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables belows.

APPENDIX 4: SUMMARY OF THE CHOI CRITERIA

Response	Definition
CR	Disappearance of all lesions
	No new lesions
PR	A decrease in size ≥10% or a decrease in tumour attenuation (HU) ≥15% on CT
	No new lesions
	No obvious progression of non-measurable disease
SD	Does not meet criteria for CR, PR, or PD
	No symptomatic deterioration attributed to tumour progression
PD	An increase in tumour size ≥10% and does not meet criteria of PR by tumour attenuation on CT
	New lesions

Abbreviations: CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; HU=Hounsfield unit.

APPENDIX 5: REPORTING OF AN EXPECTED OR UNEXPECTED SERIOUS ADVERSE EVENT (ESAE)

Serious Adverse Event Notification Form

TO BE FAXED TO THE R&D UNICANCER SAFETY DEPARTMENT – PARIS OFFICE N°+ 33 (0)1 44 23 55 70

PROTOCOL :**CYCLIGIST**	EUDRACT/ ID-RCB N°:**2013-000283-28**	COUNTRY: France
SPONSOR IDENTIFICATION N°:	**INVESTIGATOR SITE :**	**SITE N°:**
DATE OF THIS REPORT: |____|____|_____|	INITIAL REPORT ☐ / FOLLOW-UP REPORT N°|____| / FINAL REPORT ☐	

1. PATIENT IDENTIFICATION

INCLUSION N°: |_____| SURNAME (3 LETTERS): |_____| 1ST NAME (2 LETTERS): |____| DATE OF BIRTH: |____||____||_____|

TREATMENT ARM: |___| DOSE LEVEL (PHASE I STUDY): |___|

GENDER: F ☐ M ☐ WEIGHT (KG): |_____| HEIGHT (CM): |_____| BODY SURFACE AREA (M²): |___| . |____|

2. INFORMATION ON EVENT

DATE OF ONSET: |____||____||_____| TOXICITY (NCI–CTC GRADE): 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

DIAGNOSIS *OR MAIN SYMPTOM*: **only one diagnosis or one symptom** (except for linked symptoms) .....

.....

.....

DESCRIBE EVENT AND TREATMENT GIVEN (INCLUDING RELEVANT TEST/LAB DATA): .....

.....

.....

3. SERIOUSNESS CRITERIA

☐ DEATH, DATE OF DEATH: .....|____||____||_____|

☐ LIFE-THREATENING

☐ REQUIRING/PROLONGING HOSPITALIZATION (> 24H) :

DATE OF ADMISSION: .....|____||____||_____|

☐ PERSISTENT/SIGNIFICANT DISABILITY/INCAPACITY

☐ CONGENITAL DISORDER/BIRTH DEFECT

☐ MEDICALLY RELEVANT

4. OUTCOME

☐ ONGOING EVENT ☐ UNKNOWN OUTCOME

☐ RECOVERED WITHOUT SEQUELAE, ☞ DATE |____||____||_____|

☐ RECOVERED WITH SEQUELAE, ☞ DATE |____||____||_____|

SPECIFY SEQUELAE: .....

.....

☐ DEATH RELATED TO THIS EVENT, ☞ DATE |____||____||_____|

☐ DEATH UNRELATED TO THIS EVENT, ☞ DATE |____||____||_____|

CAUSE OF DEATH:.....

.....

OR CAUSE UNKNOWN ☐

☐ AUTOPSY: YES ☐ NO ☐

IF PATIENT WAS HOSPITALIZED: DATE OF END OF HOSPITALIZATION: |____||____||_____|

OR PATIENT STILL HOSPITALIZED AT TIME OF THIS REPORT ☐

FOR IMP TRIALS ☞ COMPLETE **SECTION 5** FOR RADIOTHERAPY TRIALS ☞ COMPLETE **SECTION 6** FOR OTHER NON IMP TRIALS ☞ COMPLETE **SECTION 7**

5. IMP (INVESTIGATIONAL MEDICINAL PRODUCT(S), including combined RADIOTHERAPY / SURGERY...) ..... TICK IF NA ☐

INVESTIGATIONAL PROCEDURE(S) INDICATE THE INTERNATIONAL COMMON DENOMINATION OF THE IMP & OTHER COMBINED	ROUTE	SAE CYCLE NUMBER	DATES		DOSE & UNIT			
			DATE OF FIRST ADMINISTRATION/USE (1ST DAY OF 1ST CYCLE)	DATE OF LAST ADMINISTRATION/USE BEFORE SAE	LAST DOSE ADMINISTERED BEFORE SAE		CUMULATIVE DOSE SINCE THE 1ST ADMINISTRATION	
					DOSE	UNIT	DOSE	UNIT
1.			|____|____|_____|	|____|____|_____|				
2.			|____|____|_____|	|____|____|_____|				
3.			|____|____|_____|	|____|____|_____|				
4.			|____|____|_____|	|____|____|_____|				
5.			|____|____|_____|	|____|____|_____|				
6			|____|____|_____|	|____|____|_____|				
7.			|____|____|_____|	|____|____|_____|				

UNBLINDING : YES ☐ NO ☐ NA ☐

HAS ONE (OR SEVERAL) INVESTIGATIONAL PRODUCT(S) BEEN STOPPED?

☐ YES N°|_| N°|_| N°|_|N°|_| N°|_| N°|_| N°|_| ☐ NO ☐ NA

DID THE EVENT DISAPPEAR AFTER INVESTIGATIONAL PRODUCT(S) IS STOPPED?

☐ YES ☐ NO ☐ NA

HAS ONE (OR SEVERAL) INVESTIGATIONAL PRODUCT(S) BEEN REINTRODUCED?

☐ YES N°|_| N°|_| N°|_|N°|_| N°|_| N°|_| N°|_| ☐ NO ☐ NA

DID THE EVENT REAPPEAR AFTER INVESTIGATIONAL PRODUCT(S) REINTRODUCTION?

☐ YES ☐ NO ☐ NA

Serious Adverse Event Notification Form

TO BE FAXED TO THE R&D UNICANCER SAFETY DEPARTMENT – PARIS OFFICE N°+ 33 (0)1 44 23 55 70

PROTOCOL :**CYCLIGIST**	EUDRACT/ ID-RCB N°:**2013-000283-28**		COUNTRY:
SPONSOR IDENTIFICATION N°:	**INVESTIGATOR SITE :**		**SITE N°:**
DATE OF THIS REPORT: |___|___|_____|	**INITIAL REPORT ☐**	**FOLLOW-UP REPORT N°**|___|	**FINAL REPORT ☐**
INCLUSION N°: |_____| SURNAME (3 LETTERS): |___| 1ST NAME (2 LETTERS): |___| DATE OF BIRTH : |___|___|_____|			

6. RADIOTHERAPY ..... TICK IF NA ☐

		DATES		DOSE (GY)	
TECHNIQUE	FIELD(S)	DATE OF FIRST ADMINISTRATION	DATE OF LAST ADMINISTRATION	LAST DOSE ADMINISTERED BEFORE SAE (GY)	CUMULATIVE DOSE SINCE THE 1ST ADMINISTRATION (GY)
		|___|___|_____|	|___|___|_____|		
		|___|___|_____|	|___|___|_____|		
		|___|___|_____|	|___|___|_____|		
		|___|___|_____|	|___|___|_____|		

MACHINE (SPECIFY IF POSSIBLE TRADE NAME / MODEL/SERIAL NUMBER): .....

.....

HAS RADIOTHERAPY BEEN STOPPED?	HAS RADIOTHERAPY BEEN REINTRODUCED?
☐ YES ☐ NO ☐ NA	☐ YES ☐ NO ☐ NA
DID THE EVENT DISAPPEAR AFTER RADIOTHERAPY IS STOPPED?	DID THE EVENT REAPPEAR AFTER RADIOTHERAPY REINTRODUCTION?
☐ YES ☐ NO ☐ NA	☐ YES ☐ NO ☐ NA

SCENE OF EVENT: ☐ INVESTIGATOR SITE ☐ HOME ☐ HOSPITAL ☐ DAY HOSPITAL ☐ CONVALESCENT HOME
☐ OTHER: .....

7. MEDICAL DEVICE or NON MEDICINAL PRODUCT, METHOD or ACTION ..... TICK IF NA ☐

DEVICE / Non Medicinal Product, Method or Action	DATES OF USE
COMMON DENOMINATION : TRADE NAME (IF EC MARKING) :	START DATE: |__|__|_____| STOP DATE: |__|__|_____|
MODEL :	VERSION (INCLUDED SOFTWARE) :
SERIAL NUMBER :	AND/OR BATCH NUMBER :
INDICATION OF USE FOR THE PATIENT :	

HAS DEVICE OR ONE (OR SEVERAL) PRODUCTS(S), METHOD(S) OR ACTION(S) BEEN STOPPED?	HAS DEVICE OR ONE (OR SEVERAL) PRODUCT(S), METHOD(S) OR ACTION(S) BEEN REINTRODUCED?
☐ YES ☐ NO ☐ NA	☐ YES ☐ NO ☐ NA
DID THE EVENT DISAPPEAR AFTER STOP?	DID THE EVENT REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA	☐ YES ☐ NO ☐ NA

SCENE OF EVENT: ☐ INVESTIGATOR SITE ☐ HOME ☐ HOSPITAL ☐ DAY HOSPITAL ☐ CONVALESCENT HOME
☐ OTHER, SPECIFY: .....

Serious Adverse Event Notification Form

TO BE FAXED TO THE R&D UNICANCER SAFETY DEPARTMENT – PARIS OFFICE N°+ 33 (0)1 44 23 55 70

PROTOCOL :**CYCLIGIST**	EUDRACT/ ID-RCB N°:**2013-000283-28**	COUNTRY:
SPONSOR IDENTIFICATION N°:	**INVESTIGATOR SITE :**	**SITE N°:**
DATE OF THIS REPORT: |___|___|_____|	INITIAL REPORT ☐ / FOLLOW-UP REPORT N°|___|	FINAL REPORT ☐
INCLUSION N°: |_____| SURNAME (3 LETTERS): |___| 1ST NAME (2 LETTERS): |___| DATE OF BIRTH : |___|___|_____|		

8. CONCOMITANT DRUG(S) – (EXCLUDE THOSE USED TO TREAT REACTION)

CONCOMITANT DRUG	ROUTE	START DATE	STOP DATE	ONGOING	INDICATION
1.		FROM |__|__|__|	TO |__|__|__|	☐	
2.		FROM |__|__|__|	TO |__|__|__|	☐	
3.		FROM |__|__|__|	TO |__|__|__|	☐	
4.		FROM |__|__|__|	TO |__|__|__|	☐	

9. OTHER RELEVANT HISTORY (E.G. DIAGNOSTICS, ALLERGIES, PREGNANCY WITH LAST MONTH OF PERIOD, ETC…)

.....

.....

.....

10. ASSESSMENT: IN YOUR OPINION (INVESTIGATOR), THIS EVENT IS RELATED TO (TICK ONLY ONE BOX):

☐ IMP (INVESTIGATIONAL MEDICINAL PRODUCT(S) INCLUDING COMBINED RADIOTHERAPY / SURGERY)
SPECIFY THE IMP NUMBER(S) (SEE SECTION 5 OF THE FORM): N°|_| N°|_| N°|_| N°|_| N°|_| N°|_| N°|_|
☐ INVESTIGATIONAL RADIOTHERAPY,
☐ INVESTIGATIONAL MEDICAL DEVICE OR NON MEDICINAL PRODUCT, METHOD OR ACTION

IF NOT RELATED TO EITHER INVESTIGATIONAL MP / RADIOTHERAPY / SURGERY, NMP, OR MD, **PLEASE SPECIFY** (TICK ONLY ONE BOX)

☐ PROTOCOL
☐ CONCOMITANT TREATMENT(S), SPECIFY: .....
☐ CONCOMITANT DISEASE(S), SPECIFY: .....
☐ OTHER, SPECIFY: .....

11. SAE NOTIFICATED BY:

NAME:
FUNCTION:
ADDRESS:
PHONE: ..... FAX: .....
E-MAIL: .....
DATE |___|/|___|/|_____|

SIGNATURE: .....

INVESTIGATOR

NAME:
DEPARTMENT:

DATE |___|/|___|/|_____|

SIGNATURE: .....

SPONSOR ONLY (DO NOT FULFIL THIS PART)

SPONSOR IDENTIFICATION NUMBER: .....
DATE OF RECEIPT: |___|/|___|/|_____| DATE OF THIS REPORT: |___|/|___|/|_____|

ASSESSMENT (Tick only one box):

1 ☐ INVESTIGATIONAL **MP** (INCLUDING COMBINED RADIOTHERAPY / SURGERY)
☐SPECIFY THE NUMBER(S)° N° |_| N° |_| N° |_| N° |_| N°|_| N°|_| N°|_|
2 ☐ INVESTIGATIONAL **RADIOTHERAPY,**
3 ☐ INVESTIGATIONAL **MEDICAL DEVICE OR NON MEDICINAL PRODUCT, METHOD OR ACTION**

☐IS IT A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (**SUSAR**)?
YES ☐ NO ☐

IF NOT RELATED TO EITHER 1, 2 OR 3, PLEASE SPECIFY (TICK ONLY ONE BOX)

4 ☐ PROTOCOL
5 ☐ CONCOMITANT TREATMENT(S)
6 ☐ CONCOMITANT DISEASE(S), SPECIFY .....
7 ☐ OTHER, SPECIFY .....

DATE |___|/|___|/|_____| NAME ..... SIGNATURE : .....

APPENDIX 6: PREGNANCY REPORT FORM

Pregnancy Notification Form

TO BE FAXED TO THE R&D UNICANCER SAFETY DEPARTMENT – PARIS OFFICE N°+ 33 (0)1 44 23 55 70

PROTOCOL :**CYCLIGIST**	EUDRACT/ ID-RCB N°:**2013-000283-28**	COUNTRY: France
SPONSOR IDENTIFICATION N°:	**INVESTIGATOR SITE :**	**SITE N°:**
DATE OF THIS REPORT: |___|___|___|___|___|___|	**INITIAL REPORT ☐** / **FOLLOW-UP REPORT N°**|___|	**FINAL REPORT ☐**

1. PATIENT IDENTIFICATION

INCLUSION N°: |_____|

SURNAME (3 LETTERS): |___|___|___| 1ST NAME (2 LETTERS): |___|___| DATE OF BIRTH (DD/MM/AAAA): |___|___||___|___||___|___|___|___|

TREATMENT ARM: |___| DOSE LEVEL (ONLY FOR PHASE I STUDIES): |___|

GENDER: FEMALE ☐

MALE ☐

2. INFORMATION ON PREGNANT

THE PREGNANT IS: THE PATIENT ☐

A PATIENT PARTNER ☐ ☞ SPECIFY INITIALS: |___|___| DATE OF BIRTH (DD/MM/AAAA): |___|___||___|___||___|___|___|___|

DATE OF LAST MENSTRUAL PERIOD (DD/MM/AAAA): |___|___||___|___||___|___|___|___|

ESTIMATED DATE OF DELIVERY (DD/MM/AAAA): |___|___||___|___||___|___|___|___|

WAS THE PATIENT USING CONTRACEPTION? YES ☐ NO ☐

DESCRIBE ALL RELEVANT TREATMENTS ADMINISTERED TO THE PREGNANT AND HER PARTNER IF APPLICABLE (DATE AND DOSE OF INVESTIGATIONAL DRUGS AND CONCOMITANT TREATMENTS): .....

.....

.....

.....

.....

PARENTS RELEVANT MEDICAL HISTORY:

MOTHER: .....

.....

.....

FATHER: .....

.....

.....

3. FOLLOW-UP INFORMATION

FOLLOW-UP INFORMATION CAN BE OBTAINED FROM:

DOCTOR: .....

INSTITUTION: .....

ADDRESS: .....

E-MAIL: .....

PHONE: ..... FAX: .....

4. INVESTIGATOR

NAME:.....

DEPARTMENT: .....

PHONE: .....

FAX: .....

E-MAIL: .....

DATE (DD/MM/AAAA): |__|__|/|__|__|/|__|__|__|__|: SIGNATURE: .....

APPENDIX 7: PRE-SCREENING FORM

INSTITUT BERGONIÉ
229 cours de l'Argonne
CS 61283 - 33076 Bordeaux cedex
www.bergonie.org
CENTRE RÉGIONAL DE LUTTE CONTRE LE CANCER DE BORDEAUX ET DU SUD-OUEST
UNICANCER MEMBRE DU GROUPE

CYCLIGIST study

PRE-SCREENING FORM

PRE-SCREENING REGISTRATION REQUEST FORM

Investigational site	
N° Center : |__|__|	**Investigator:**
Tel: |__|__|.|__|__|.|__|__|.|__|__|.|__|__|.|__|__|	Fax: |__|__|.|__|__|.|__|__|.|__|__|.|__|__|

Patient		
Patient: |__|__| |__|__| Name First Name	Birth Date: |__|__|/ |__|__|/ |__|__|__|__| (DD/MM/YYYY)	Sex: ❑ **M** ❑ **F**
Date of signed consent patient: |__|__|/ |__|__|/ |__|__|__|__| (DD/MM/YYYY)		

Does the patient accept to participate at the translational study ❑ **Yes** ❑ **No**	
Date of signed optional consent patient : |__|__|/ |__|__|/ |__|__|__|__| (DD/MM/YYYY)	

Warning: should be sent **within 7 days** for array-CGH analysis and diagnosis of GIST if necessary :

- Pre-Screening pathology request form completed
- FFPE (Formalin-Fixed Paraffin-Embedded) of initial block of specimen tumor sampling
- Initial pathology report with patient code and date of birth (including macroscopic description) and pathology report of molecular biology

Fax and/or e-mail this form to:

Clinical Trial and Epidemiology Unit / Institut Bergonié

Fax: + 33 5 56 33 04 85

From Monday to Friday : 9.00AM to 5.00PM

Contact : David JUZANX - Tel : + 33 5 24.07.19.25 – Mail: d.juzanx@bordeaux.unicancer.fr
and Sabrina SELLAN-ALBERT (CRA Back-up), Mail – s.albert@bordeaux.unicancer.fr

Screening Registration (coordinator centre)

Date of registration: |__|__|/ |__|__|/ |__|__|__|__| (DD/MM/YYYY)

Patient pre-screening number in this study: |__|__|__|

Cycligist Study - Pre-Screening Form - Version 2 -06.12.2013-

APPENDIX 8: REGISTRATION FORM

INSTITUT BERGONIÉ
229 cours de l'Argonne
CS 61283 - 33076 Bordeaux cedex
www.bergonie.org

CYCLIGIST study

REGISTRATION FORM

INCLUSION REQUEST FORM

Investigational site	
N° Center : |__|__|	**Investigator:**
Tel: |__|__|.|__|__|.|__|__|.|__|__|.|__|__|	Fax: |__|__|.|__|__|.|__|__|.|__|__|.|__|__|

Patient		
Patient: |__|__| |__|__| Name First Name	**Birth Date:** |__|__|/ |__|__|/ |__|__|__|__| (DD/MM/YYYY)	Sex: ☐ M ☐ F
Patient screening number: |__|__|__|		

Confirmation of eligibility criteria: ☐ **Yes** ☐ **No**	
Date foreseen for protocol treatment start:..... |__|__|/ |__|__|/ |__|__|__|__| (DD/MM/YYYY)	
Date of signed consent patient: |__|__|/ |__|__|/ |__|__|__|__| (DD/MM/YYYY)	**To confirm inclusion, signed investigator:**

Does the patient accept to participate at the translational study ☐ **Yes** ☐ **No**
Date of signed optional consent patient : ..... |__|__|/ |__|__|/ |__|__|__|__| (DD/MM/YYYY)

Fax and/or e-mail this form to:
Clinical Trial and Epidemiology Unit / Institut Bergonié
Fax: + 33 5 56 33 04 85
From Monday to Friday : 9.00AM to 5.00PM
Contact : David JUZANX - Tel : + 33 5 24.07.19.25 – Mail: d.juzanx@bordeaux.unicancer.fr
and Sabrina SELLAN-ALBERT (CRA Back-up), Mail – s.albert@bordeaux.unicancer.fr

Inclusion Registration (coordinator centre)
Date of inclusion: |__|__|/ |__|__|/ |__|__|__|__| (DD/MM/YYYY)
Patient identification number in this study: |__|__|

Cycligist Study - Registration Form - Version 2 -06.12.2013-

APPENDIX 9: PATHOLOGY REQUEST FORM

INSTITUT BERGONIÉ
229 cours de l'Argonne
CS 61283 - 33076 Bordeaux cedex
www.bergonie.org
CENTRE RÉGIONAL DE LUTTE CONTRE LE CANCER DE BORDEAUX ET DU SUD-OUEST
UNICANCER MEMBRE DU GROUPE

CYCLIGIST study

PATHOLOGY FORM

PRE SCREENING PATHOLOGY REQUEST FORM

PRE-SCREENING N°: |__|__|__|	**Center** : |__|__|

To be handled by the entering clinician:
Please send this form for every registered patient.

The protocol requires an analysis of CDKN2A gene deletion assessed by array-comparative genomic hybridization (array-CGH).
You are kindly requested to submit, **within 7 days following signed informed consent** :

- One or two FFPE (Formalin-Fixed Paraffin-Embedded) blocks
- Pathology report with patient code and date of birth (including your macroscopic description) and pathology report of molecular biology

From: (Clinician) _____

(Hospital address) _____

Patient : |__|__| |__|__| Date of birth |__|__| |__|__| |__|__| (DD, MM, YY) Sex : ❑ Male ❑ Female
Name First Name

References of anatomopathology block sent _____

Site of tumor/biopsy: _____

➢ Diagnostic of GIST confirmed by the RRePS Network : ❑ Yes ❑ No

I certify that this information is complete and matches the accompanying media.
Name of the Person Completing this Form: _____Date: _____
Title of Person Completing Form: _____

RESPONSE OF CENTRAL PATHOLOGY DEPARTMENT

Diagnostic of GIST : In case of the diagnosis was not confirmed by the RRePS Network, diagnosis review by central pathological : confirmation of GIST : ❑ Yes ❑ No

Date of histological review (dd/mm/yyyy): |__|__| |__|__| |__|__|__|__|

Name of the Person Completing this Response Form: _____

Title of Person Completing Form: _____Signature: _____

Analysis of array-CGH : Deletion of P16 gene: ❑ Yes ❑ No ❑ No interpretable
❑ Homozygous ❑ Heterozygous

Deletion of RB gene: ❑ Yes ❑ No ❑ No interpretable
❑ Homozygous ❑ Heterozygous

⚠ **Patient must have homozygous or heterozygous deletion of P16 gene AND no deletion or heterozygous deletion of RB gene**

Conclusion : incluable patient ❑ Yes ❑ No Date (dd/mm/yyyy): |__|__| |__|__| |__|__|__|__|

Name of the Person Completing this Response Form: _____

Title of Person Completing Form: _____Signature: _____

Please send this form to: Institut Bergonié-Service Pathologie Technicienne Anapath Protocole CYCLIGIST 229 cours de l'Argonne-33076 Bordeaux Cedex, France Tél: 05.56.33.78.53 – mail : m.louty@bordeaux.unicancer.fr	All the material will be returned. Everything requested in this form was accepted by the patient. Thanks in advance for your co-operation.

Cycligist Study - Pathology Form - Version 2 -09.04.2015-

APPENDIX 10: OPTIONAL PATHOLOGY REQUEST FORM

INSTITUT BERGONIÉ
229 cours de l'Argonne
CS 61283 - 33076 Bordeaux cedex
www.bergonie.org
CENTRE RÉGIONAL DE LUTTE CONTRE LE CANCER DE BORDEAUX ET DU SUD-OUEST
UNICANCER MEMBRE DU GROUPE

CYCLIGIST study

OPTIONAL PATHOLOGY FORM

OPTIONAL PATHOLOGY REQUEST FORM

Center : |__|__|	**INCLUSION N°:** |__|__|

To be handled by the entering clinician:
Please send this form for every registered patient who signed informed consent optional study, with:.

- Tumor biopsies performed at Day –3 to Day -1 and Day 21 Cycle 1
- Pathology report with patient code and date of birth if available

Each site will send samples to Bergonie Institute

From: (Clinician) _____

(Hospital address) _____

Patient : |__|__| |__|__| Date of birth |__|__| |__|__| |__|__| (DD, MM, YY) Sex : ❑ Male ❑ Female
Name First Name

Date of biopsy |__|__| |__|__| |__|__| Tumor biopsy : ❑ Day -3 to Day -1

❑ Day 21 Cycle 1

Fixative of biopsy sample: ❑ FFPE (Formalin-Fixed Paraffin-Embedded)

❑ Other : specify _____

References of anatomopathology block sent _____

Site of tumor/biopsy: _____

Pathology report available : ❑ Yes ❑ No

I certify that this information is complete and matches the accompanying media.

Name of the Person Completing this Form: _____Date: _____

Title of Person Completing Form: _____

Please send this form to: Institut Bergonié-Service Pathologie- Technicienne Anapath Protocole CYCLIGIST 229 cours de l'Argonne-33076 Bordeaux Cedex, France Tél: 05.56.33.78.53 – mail : m.louty@bordeaux.unicancer.fr	Everything requested in this form was accepted by the patient. Thanks in advance for your co-operation.

Cycligist Study – Optional Pathology Form - Version 2 -05.05.2015-

APPENDIX 11: BASELINE CLINICAL SUBJECT PROFILE

INSTITUT BERGONIÉ
229 cours de l'Argonne
CS 61283 - 33076 Bordeaux cedex
www.bergonie.org

CYCLIGIST study

BASELINE CLINICAL SUBJECT PROFILE

PRE-SCREENING N°: |__|__|__|	Centre : |__|__|

To be completed by the Investigator:
In case of progression's confirmation, this subject is enrolled in a clinical trial that will rely on an Independent Review. To ensure benign lesions are not selected by the independent reviewers as sites of metastatic disease, identify any pre-existing (pre-baseline) radiographic findings that could mimic metastatic disease and any major alterations resulting from prior surgery or interventional procedures.

Are there any conditions that meet the above criteria which mimic metastatic disease?

❑ **YES** ❑ **NO**

If yes, please specify Anatomic Description :

.....

.....

.....

Radiation therapy history:

Has the patient received radiation therapy? ❑ No ❑ Yes If "Yes", please answer questions below:

Anatomical fields (please specify Left or Right when necessary):

(1) _____
(2) _____
(3) _____

I certify that this information is complete and matches the accompanying media.

Name of the Person Completing this Form: _____ Date: _____

Title of Person Completing Form: _____

This completed form must be sent with the first "Radiology Referral Form-Baseline" to:

David Juzanx
Clinical Research Assistant
Institut Bergonié – 229 cours de l'Argonne – 33076 Bordeaux Cedex, France
Phone: +33 5 24 07 19 25 – Mail: d.juzanx@bordeaux.unicancer.fr

APPENDIX 12: RADIOLOGY REFERRAL FORM

INSTITUT BERGONIÉ
229 cours de l'Argonne
CS 61283 - 33076 Bordeaux cedex
www.bergonie.org

CYCLIGIST study

RADIOLOGY REFERRAL FORM

PRE-SCREENING N°: |__|__|__| OR **PATIENT N°:** |__|__|	**Centre:** |__|__|

Time Point designation: ❑ Baseline ❑ Week #4 ❑ Week #8 ❑4-months ❑ Week # __

To be completed by the Investigator:
This subject is enrolled in a clinical trial that will rely on an Independent Review. For consistency, the same method of assessment and the same technique should be used at baseline and during study.

- Reviewing the progressive disease status at baseline (two imaging CDs will be sent)
- Reviewing the disease status at 4-months in comparison with baseline and week#16
- Reviewing all responses (complete and partial) observed during study.

Patient' files will be anonymous
Media should be accompanied by the completed form.

Imaging Exams Performed	**Exam Date** (dd/mm/yyyy)
CT: ❑ Chest ❑ Abdomen ❑ Pelvis ❑ Other (please specify):	__ __/__ __/__ __ __ __
MRI: ❑ Chest ❑ Abdomen ❑ Pelvis ❑ Other (please specify):	__ __/__ __/__ __ __ __

I certify that this information is complete and matches the accompanying media.
Name of the Person Completing this Form: _____ Date: _____
Title of Person Completing Form: _____

All CDs and this completed form must be sent to:

David Juzanx
Clinical Research Assistant
Institut Bergonié – 229 cours de l'Argonne – 33076 Bordeaux Cedex, France
Phone: +33 5 24 07 19 25 – Mail: d.juzanx@bordeaux.unicancer.fr

Cycligist Study - RADIOLOGY REFERRAL FORM - Version 1 -17.01.2013-

APPENDIX 13: BASELINE RADIOLOGY REVIEW FORM

INSTITUT BERGONIÉ
229 cours de l'Argonne
CS 61283 - 33076 Bordeaux cedex
www.bergonie.org

CYCLIGIST study

RADIOLOGY REVIEW FORM
-Baseline-

PATIENT : Name |__|__| First Name |__|__|		**Centre :** |__|__|		
PRE-SCREENING n°: |__|__|__|				
	Targets evaluation (mm)	**Sum RECIST (mm)**	**% Evaluation**	**Response**
INCLUSION 1 **Date** |__|__|/|__|__|/|__|__|__|__| **Target 1:**…… **Target 2:**…… **Target 3:**…… **Target 4:**…… **Target 5:**……	T1: |__|__|__| T2: |__|__|__| T3: |__|__|__| T4: |__|__|__| T5: |__|__|__|	|__|__|__|		
Non-target lesions				
INCLUSION 2 : **Date** |__|__|/|__|__|/|__|__|__|__| **Target 1:**…… **Target 2:**…… **Target 3:**…… **Target 4:**…… **Target 5:**……	T1: |__|__|__| T2: |__|__|__| T3: |__|__|__| T4: |__|__|__| T5: |__|__|__|	|__|__|__|	❑+ |__|__|__| ❑−	1 = CR 2 = PR 3 = SD |__| 4 = PD 5 = NE
Non-target lesions	1 = CR 2 = PD |__| 3 = SD 4 = NE			
New lesions	1 = Oui |__| 2 = Non			

Comments :

_____

Reviewer's name: _____ Signature: _____

Date of central review: \|__\|__\|/\|__\|__\|/\|__\|__\|__\|__\|

Cycligist Study - RADIOLOGY REVIEW FORM-BASELINE Version 1 -17.01.2013

APPENDIX 14: INFORMED CONSENT – PRINCIPAL STUDY

Note d'information destinée aux personnes participant au protocole de Recherche Biomédicale « CYCLIGIST »

Etude principale

Titre de l'essai : Efficacité et tolérance du PD-0332991 chez les patients atteints d'une Tumeur Stromale Gastro-intestinale (GIST) localement avancée, réfractaire à Imatinib et Sunitinib : essai de phase 2

Promoteur : Institut Bergonié, 229 Cours de l'Argonne, 33076 BORDEAUX Cedex.

Investigateur Coordonnateur : Dr Antoine ITALIANO, Département d'Oncologie Médicale, Institut Bergonié, 229 Cours de l'Argonne, 33076 BORDEAUX Cedex.

Madame, Mademoiselle, Monsieur,

Votre médecin vous propose de participer à une recherche biomédicale dont le nom du promoteur est l'Institut Bergonié. Avant de prendre une décision, il est important que vous lisiez attentivement ces pages qui vous apporteront les informations nécessaires concernant les différents aspects de cette recherche. N'hésitez pas à poser à votre médecin toutes les questions que vous jugerez utiles.

Votre médecin vous a expliqué que vous étiez porteur d'une tumeur stromale gastro-intestinale, un cancer du système digestif qui touche 600 à 900 nouvelles personnes par an en France, plus couramment appelée GIST (pour Gastro Intestinal Stromal Tumor en anglais). Dans votre cas, cette tumeur est évolutive. Nous vous proposons de participer à un protocole de traitement concernant votre maladie.

Votre participation est entièrement volontaire. Si vous ne désirez pas prendre part à cette recherche, vous continuerez à bénéficier de la meilleure prise en charge médicale possible, conformément aux connaissances actuelles.

Pourquoi mon médecin me propose-t-il de participer à cette étude ?

Nous vous proposons cette étude car vous avez une tumeur stromale gastro-intestinale nécessitant un traitement médical.

Le PD-0332991 est une molécule développée par les Laboratoires Pfizer et qui a la propriété d'inhiber la croissance des tumeurs. Des données scientifiques récentes permettent de penser que ce médicament est efficace dans le traitement des tumeurs stromale gastro-intestinale évolutives.

L'objectif de cette étude est donc d'évaluer l'efficacité et la tolérance (effets secondaires) du PD-0332991 dans le traitement des tumeurs stromales gastro-intestinales évolutives.

Comment cette étude se déroule-t-elle ?

Elle prévoit la participation d'environ 63 patients de 10 centres français qui seront inclus sur une durée estimée à 18 mois.

Avant d'entrer dans l'étude…

Pour participer à cette étude, vous devez être bénéficiaire d'un régime de sécurité sociale en tant qu'assuré ou ayant-droit. Vous ne serez inclus dans l'étude que si vous datez et signez le

consentement qui vous est remis. Vous ne pourrez participer en même temps à une autre recherche biomédicale. Vous pouvez ensuite vous retirer à tout moment de l'essai sans justification, sans conséquence sur la suite de votre traitement ni sur la qualité des soins qui vous seront fournis et sans conséquence sur la relation avec votre médecin ; vous pourrez être suivi par la même équipe médicale.

Si vous souhaitez participer à cette étude, nous vous demandons de signer un formulaire de consentement de participation attestant simplement que vous avez été informé(e) de cette étude et que vous y participez librement. Vous en conserverez un exemplaire.

Vous serez ensuite enregistré comme participant et des analyses et examens seront effectués afin de déterminer si vous pouvez recevoir le traitement (examen clinique, prélèvements sanguins, test de grossesse si vous êtes une femme en âge d'avoir des enfants, électrocardiogramme et scanner ou IRM).

Si les résultats de ces divers examens vous permettent de participer à cette étude en toute sécurité, vous pourrez commencer le traitement par PD-0332991.

Durant l'étude…

D'autres examens habituellement réalisés en routine dans ce type de prise en charge, seront effectués pendant la durée de votre traitement :

A chaque visite les examens suivant seront réalisés :

- un examen clinique toutes les 4 semaines,
- des bilans sanguins seront réalisés à la 2ème semaine de traitement du cycle 1, puis toutes les 4 semaines pendant les 6 premiers mois, et toutes les 8 semaines après 6 mois de traitement,
- scanner ou IRM toutes les 8 semaines,
- et tout autre examen ou procédure que votre médecin jugera nécessaire dans votre intérêt.

Quand vous aurez terminé le traitement…

Dans le cadre de la surveillance de votre état de santé et de votre maladie, vous aurez une visite avec votre médecin pour un examen clinique et un prélèvement sanguin 4 semaines après la dernière prise du médicament.

Le déroulement de l'étude est résumé ci-dessous :

Dans cette étude, vous allez prendre le médicament PD-0332991 tous les jours pendant 21 jours consécutifs et le stopper durant 7 jours complets ensuite. Cette période de 28 jours est appelée un cycle. Vous devrez prendre le médicament ainsi pour chaque cycle de traitement.

Lors du suivi de l'étude et dans certains cas (progression de votre maladie), votre médecin pourra décider d'interrompre le traitement en cours.

Le schéma ci-après vous montre ce qu'il se passera durant ces cycles.

	Avant le début du traitement		Cycle 1		Cycle n	Fin de traitement	Suivi
Visites			**V1**	**V2**	**Vn**		
Jours de cycle		1 à 21 jours avant le début du traitement	Jour 1	Jour 15	Jour 1	Dans les 28 jours après arrêt du traitement	
Note information et consentement	X						
Analyse génomique	X						
Historique							
Données du patient (Age, sexe..)		X					
Critères inclusion/exclusion		X					
Antécédents médicaux pertinents / Etat de santé actuel		X					
Diagnostic tumoral		X					
Traitements antineoplastiques antérieurs		X					
Traitements concomitants		X	En continu jusqu'à 28 jours après la dernière dose du traitement à l'étude				
Traitement antinéoplasique depuis arrêt du traitement à l'étude							X
Examen clinique							
Examen physique		X	X	X	X	X	
Taille/Poids		X	X	X	X	X	
Signes vitaux		X	X	X	X	X	
Examens de laboratoire							
Hematologie		X	X	X	X Jour 1 et 15	X	
Biochimie		X	X	X	X	X	
Coagulation		X	X	X	X	X	
Test de grossesse si applicable		X	X		X	X	
Imagerie/Autre examen							
Evaluation tumorale CT scan ou IRM			Jour 28 du Cycle 1, Jour 28 du Cycle 2 puis toutes les 8 semaines jusqu'au 6ème mois. Ensuite toutes les 12 semaines				
ECG		X	X	X	X	X	
Tolérance							
Effets indésirables			En continu jusqu'à 28 jours après la dernière dose du traitement à l'étude				
Biomarqueurs							
Biopsie tumorale (optionnel) Jour –3 à Jour -1 et Jour 21 cycle 1		1 à 3 jours avant le début du traitement	Jour 21 du Cycle 1				
Autres							
Administration du PD-0332991			Prise de la molécule pendant 21 jours puis arrêt pendant 7 jours				
Raison de fin de traitement						X	
Suivi tous les 3 mois pendant 1 an							X

Est-ce que je peux arrêter de participer à cette étude ?

Oui. Vous pouvez décider d'arrêter à n'importe quel moment. Appelez votre médecin si vous souhaitez arrêter le traitement.

Ensemble, vous pourrez alors discuter des risques éventuels liés à cet arrêt. Quelle que soit votre décision, votre médecin vous conseillera sur les meilleurs traitements adaptés à votre situation et vous informera du suivi des examens nécessaires.

Votre médecin peut décider à tout moment d'interrompre votre participation à l'étude s'il juge que cela est dans votre intérêt, ou si vous ne suivez pas les recommandations de l'étude, ou si l'étude est arrêtée.

Quels sont les risques prévisibles de cette étude ?

Comme tout médicament, l'administration de PD-0332991 peut être à l'origine d'effets secondaires indésirables. Peuvent ainsi survenir :

- Fatigue
- Chute des globules blancs, rouges et des plaquettes
- Nausées et/ou vomissements
- Diarrhées
- Constipation
- Eruption cutanée, sécheresse cutanée
- Essoufflement
- Perte d'appétit
- Saignement
- Frissons
- Fièvre
- Toux
- Chute des cheveux
- Œdèmes
- Infections, notamment respiratoires
- Troubles du goût
- Inflammations de la muqueuse buccale (douleurs, aphes…)
- Troubles oculaires (vision floue, larmoiement, sécheresse oculaire).

Des effets secondaires non encore identifiés pourraient également survenir.

Dans la mesure du possible, votre médecin prendra toutes les mesures nécessaires pour prévenir ou atténuer la survenue d'éventuels effets secondaires. Il pourra également diminuer la dose de traitement ou l'interrompre en cas de mauvaise tolérance ou à votre demande.

Signaler à votre médecin tout événement indésirable, que vous pensez liés ou non au traitement. Il consignera ces informations.

Votre médecin est bien sûr à votre disposition pour répondre à toutes vos demandes d'information sur les risques et effets secondaires du traitement.

Quels sont les bénéfices prévisibles de cette étude ?

Même si votre médecin espère que le traitement que vous allez recevoir sera efficace, il ne peut en avoir la certitude à l'avance. Le suivi prévu dans cette étude (bilans sanguins et radiologiques) permettra d'évaluer étroitement et régulièrement la bonne tolérance de votre traitement ainsi que son efficacité.

Quelle alternative ai-je, si je ne participe pas à cette étude ?

Vous avez parfaitement le droit de ne pas participer à cette étude. Cela n'aura aucune conséquence sur votre prise en charge et sur votre relation avec votre médecin. Dans le cas d'un refus de votre part, votre médecin conviendra avec vous de la prise en charge thérapeutique alternative la plus adaptée à votre situation.

Quels sont vos droits ?

Votre médecin doit vous fournir toutes les explications nécessaires concernant cette recherche. Si vous souhaitez vous en retirer à quelque moment que ce soit, et quel que soit le motif, vous continuerez à bénéficier du suivi médical et cela n'affectera en rien votre surveillance future.

Dans le cadre de la recherche biomédicale à laquelle l'Institut Bergonié vous propose de participer, un traitement informatique de vos données personnelles va être mis en œuvre pour permettre d'analyser les résultats de la recherche au regard de l'objectif de cette dernière qui vous a été présenté. A cette fin, les données médicales vous concernant seront transmises au promoteur de la recherche ou aux personnes ou sociétés agissant pour son compte, en France ou à l'étranger. Ces données seront identifiées par un code et/ou vos initiales. Ces données pourront également, dans des conditions assurant leur confidentialité, être transmises aux autorités de santé françaises ou étrangères et à d'autres entités de l'Institut Bergonié.

Conformément aux dispositions de la loi relative à l'informatique, aux fichiers et aux libertés, vous disposez à tout moment d'un droit d'accès et de rectification des données informatisées vous concernant (loi n° 2004-801 du 6 août 2004 modifiant la loi n° 78-17 du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés). Vous disposez également d'un droit d'opposition à la transmission des données couvertes par le secret professionnel susceptibles d'être utilisées dans le cadre de cette recherche et d'être traitées. Vous pouvez également accéder directement ou par l'intermédiaire du médecin de votre choix à l'ensemble de vos données médicales en application des dispositions de l'article L1111-7 du code de la santé publique. Ces droits s'exercent auprès du médecin qui vous suit dans le cadre de la recherche et qui connaît votre identité.

Conformément à la loi n°2004-806 du 9 août 2004 relative à la Politique de Santé Publique (art L1121-1 à L1126-6 du code de la santé publique) :
- cette recherche a obtenu un avis favorable du Comité de Protection des Personnes du Sud-Ouest et Outre-Mer III le 30/10/2013 et l'autorisation de l'Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM) le 13/11/2013.
- le promoteur de cette recherche, l'Institut Bergonié (Centre régional de Lutte Contre le Cancer du Sud-Ouest situé au 229, cours de l'Argonne, 33076 Bordeaux cedex), a souscrit une assurance de responsabilité civile auprès de HDI GERLING, TOUR OPUS 12, 77, Esplanade de la Défense 92914 Paris LA DEFENSE, n° police 0100871914011-130002-10998,
- les personnes ayant subi un préjudice après participation à une recherche biomédicale peuvent faire valoir leurs droits auprès des commissions régionales de conciliation et d'indemnisation des accidents médicaux,
- lorsque cette recherche sera terminée, vous serez tenus informés personnellement des résultats globaux par votre médecin dès que ceux-ci seront disponibles, si vous le souhaitez.

Après avoir lu cette note d'information, n'hésitez pas à poser à votre médecin toutes les questions que vous désirez. Après un délai de réflexion, si vous acceptez de participer à cette recherche, vous devez compléter et signer le formulaire de consentement de participation. Un exemplaire du document complet vous sera remis.

Le Docteur …… (Tél. ……..) se tient à votre disposition pour répondre à toutes vos éventuelles questions complémentaires.

Formulaire de recueil de consentement [1] destiné aux personnes participant au protocole de Recherche Biomédicale

« *CYCLIGIST*»

Etude principale

Titre de l'essai : Efficacité et tolérance du PD-0332991 chez les patients atteints d'une Tumeur Stromale Gastro-intestinale (GIST) localement avancé, réfractaire à Imatinib et Sunitinib : essai de phase 2

(1) Un exemplaire co-signé doit être remis à la personne qui participe à la recherche et à l'investigateur

Promoteur : Institut Bergonié, 229 Cours de l'Argonne, 33076 BORDEAUX Cedex.

Investigateur Coordonnateur : Dr Antoine ITALIANO, Département d'Oncologie Médicale, Institut Bergonié, 229 Cours de l'Argonne, 33076 BORDEAUX Cedex.

Je soussigné(e).....*(nom, prénom)* certifie avoir lu et compris la note d'information qui m'a été remise.

J'ai eu la possibilité de poser toutes les questions que je souhaitais au Pr/Dr……. *(nom, prénom)* qui m'a expliqué la nature, les objectifs, les risques potentiels et les contraintes liées à ma participation à cette recherche.

Je connais la possibilité qui m'est réservée d'interrompre ma participation à cette recherche à tout moment sans avoir à justifier ma décision et je ferai mon possible pour en informer le médecin qui me suit dans la recherche. Cela ne remettra naturellement pas en cause la qualité des soins ultérieurs.

J'ai eu l'assurance que les décisions qui s'imposent pour ma santé seront prises à tout moment, conformément à l'état actuel des connaissances médicales.

Je suis informé(e) que la possibilité qu'une partie des prélèvements effectués à l'occasion de ce protocole de recherche soit conservée pour une utilisation ultérieure à des fins de recherche. J'ai également été informé(e) de mon droit à m'opposer à ce que cette conservation et cette utilisation ultérieure à des fins de recherche aient lieu.

J'ai pris connaissance que cette recherche a reçu l'avis favorable du Comité de Protection des Personnes du Sud-Ouest et Outre-Mer III le 30/10/2013 et l'autorisation de l'ANSM le 13/11/2013 et a fait l'objet d'une déclaration à la Commission Nationale Informatique et Libertés (CNIL).

Le promoteur de la recherche l'Institut Bergonié (Centre régional de Lutte Contre le Cancer du Sud-Ouest situé au 229, cours de l'Argonne, 33076 Bordeaux cedex) a souscrit une assurance de responsabilité civile en cas de préjudice auprès de la société HDI GERLING, TOUR OPUS 12, 77, Esplanade de la Défense 92914 Paris LA DEFENSE, n° police 0100871914011-130002-10998.

J'accepte que les personnes qui collaborent à cette recherche ou qui sont mandatées par le promoteur, ainsi qu'éventuellement le représentant des Autorités de Santé, aient accès à l'information dans le respect le plus strict de la confidentialité.

J'accepte que les données enregistrées à l'occasion de cette recherche puissent faire l'objet d'un traitement informatisé sous la responsabilité du promoteur.

J'ai bien noté que, conformément aux dispositions de la loi relative à l'informatique, aux fichiers et aux libertés, je dispose d'un droit d'accès et de rectification. Je dispose également d'un droit d'opposition à la transmission des données couvertes par le secret professionnel susceptibles d'être utilisées dans le cadre de cette recherche et d'être traitées. Ces droits s'exercent auprès du médecin qui me suit dans le cadre de cette recherche et qui connaît mon identité.

Mon consentement ne décharge en rien l'investigateur et le promoteur de la recherche de leurs responsabilités à mon égard. Je conserve tous les droits garantis par la loi.

Les résultats globaux de la recherche me seront communiqués directement, si je le souhaite, conformément à la loi du 4 mars 2002 relative aux droits des malades et à la qualité du système de santé.

Ayant disposé d'un temps de réflexion suffisant avant de prendre ma décision, j'accepte librement et volontairement de participer à la recherche Cycligist /__/ ***oui*** /__/ ***non***

Je pourrai à tout moment demander des informations complémentaires au médecin qui m'a proposé de participer à cette recherche, n° téléphone :

Fait à _____ Fait à _____

Le |__|__| |__|__| |__|__|__|__| Le |__|__| |__|__| |__|__|__|__|

Signature du patient :

APPENDIX 15: INFORMED CONSENT – OPTIONAL STUDY

Note d'information destinée aux personnes participant au protocole de Recherche Biomédicale « CYCLIGIST »

Etudes biologiques optionnelles

Titre de l'essai : Efficacité et tolérance du PD-0332991 chez les patients atteints d'une Tumeur Stromale Gastro-intestinale (GIST) localement avancée, réfractaire à Imatinib et Sunitinib : essai de phase 2

Promoteur : Institut Bergonié, 229 Cours de l'Argonne, 33076 BORDEAUX Cedex.

Investigateur Coordonnateur : Dr Antoine ITALIANO, Département d'Oncologie Médicale, Institut Bergonié, 229 Cours de l'Argonne, 33076 BORDEAUX Cedex.

Madame, Mademoiselle, Monsieur,

Votre médecin va vous expliquer les détails de ce projet de recherche expérimentale qui fait partie de l'étude Cycligist.

Après avoir pris connaissance de cette note d'information, il vous sera demandé de compléter le formulaire de consentement qui est joint et qui attestera que vous avez lu les informations contenues dans ce document, que vous avez compris les modalités de ces recherches et que vous avez librement accepté d'y participer.

Vous êtes libre d'accepter ou de refuser de participer à cette recherche. Si vous êtes d'accord pour y participer, il vous sera demandé de dater et signer cette note. Sinon, cela ne vous empêche nullement de continuer votre participation à l'étude principale Cycligist.

Si vous acceptez cette étude optionnelle, une biopsie tumorale sera effectuée :

- au début de l'étude, Jour1 du cycle 1, avant l'administration de la première dose de PD-0332991.
- et au 21ème jour du Cycle 1.

A PROPOS DU DON DE TISSU POUR LA RECHERCHE :

Une partie du matériel biologique (échantillon tumoral) obtenu lors des procédures de diagnostic (biopsie ou chirurgie) que vous avez déjà eu et les biopsies complémentaires réalisées dans le cadre de cette étude, pourront être utilisés pour la recherche.

Si vous êtes d'accord, ce tissu pourra être conservé et ensuite utilisé pour améliorer les connaissances sur les tumeurs stromale gastro-intestinale.
Les recherches qui pourront être entreprises à partir de votre tumeur permettront de mieux comprendre les mécanismes d'action et les effets du PD-0332991 dans les tumeurs stromales gastro-intestinales. Elles pourront dans le futur aider les personnes atteintes du même cancer ou d'autres maladies. Les informations enregistrées à l'occasion de ces études exploratoires ne seront pas inscrites dans votre dossier médical et ne seront disponibles ni pour votre famille, ni pour votre médecin personnel, ni pour un tiers.
Cette recherche n'affectera pas votre prise en charge.

BUT DE L'ÉTUDE :

Le but de cette étude est de mieux comprendre comment et pourquoi le PD-0332991 agit ou non sur votre cancer et d'identifier des caractéristiques des cellules cancéreuses permettant de prédire l'efficacité de ce médicament. Cela permettra peut-être de mettre au point des tests qui identifieront les personnes les plus susceptibles d'avoir un bénéfice potentiel au PD-0332991 pour le traitement de leur maladie.

QUE PENSER DE VOTRE PARTICIPATION À CETTE RECHERCHE ?

Vous êtes libre d'accepter de donner vos échantillons tumoraux à la recherche. Quoi que vous décidiez, votre choix n'affectera en rien votre prise en charge.

Pendant et après l'étude, vous resterez propriétaire des échantillons et vous aurez à tout moment le droit de demander la destruction de ces échantillons en contactant votre médecin de l'étude. Si vous décidez de faire détruire vos échantillons, les informations obtenues avant votre demande ne seront pas détruites, mais aucune étude supplémentaire ne sera réalisée.
L'Institut Bergonié sera le propriétaire des données et des résultats dérivés de cette étude et sera responsable de la destruction du matériel génétique sur votre demande ou à la fin de la période de conservation. Suite à votre demande de destruction, l'Institut Bergonié confirmera par courrier à votre médecin investigateur que votre matériel génétique a été détruit.

CONFIDENTIALITE

Pour éviter toute mauvaise utilisation de ces données celles-ci resteront confidentielles.

Pour que la confidentialité soit maximale, tous les échantillons et les informations se rapportant aux échantillons seront codés pour éviter l'exposition des informations vous concernant ainsi que votre identité.

En outre, les informations qui concernent les échantillons sont conservées dans une base de données sécurisée tandis que les données génétiques sont conservées dans une base de données indépendante, elle aussi sécurisée et ne comportant aucune information relative à votre identité.

Cependant vous serez identifié par vos initiales et un code patient uniquement. Vous ne serez pas identifié dans les rapports ou les publications issus de cette étude.

Sauf si cela est exigé par les Autorités de Santé pour vérifier des informations, seul l'Institut Bergonié et les personnes autorisées par l'Institut Bergonié auront accès aux données issues de cette recherche sur les biomarqueurs. Les personnes autorisées par l'Institut Bergonié n'auront pas accès à des résultats identifiés par votre nom.

BÉNÉFICES POTENTIELS

Vous ne tirerez pas de bénéfices directs de cette étude. L'information recueillie permettra de faire avancer les connaissances médicales sur la mise au point de traitements plus efficaces et plus sûrs des cancers.

RISQUES ET DÉSAGRÉMENTS

Les biopsies seront réalisées avec toutes les précautions possibles afin de vous éviter tout désagrément. Néanmoins comme pour toute procédure médicale, des risques existent. Peuvent ainsi survenir de manière exceptionnelle :

- Malaise
- Douleur
- Saignement
- Infection
- Ponction potentiellement grave et non désirée d'autres organes

En cas de complication, votre médecin mettra tout en œuvre pour vous soigner et éviter toute séquelle.

PROTECTION DES PERSONNES PARTICIPANT A L'ETUDE

Pour participer à cette étude, vous devez être bénéficiaire d'un régime de sécurité sociale en tant qu'assuré ou ayant-droit. Vous ne serez inclus dans l'étude que si vous datez et signez ce consentement qui vous est remis. Vous ne pourrez participer en même temps à une autre recherche biomédicale. Vous pouvez ensuite vous retirer à tout moment de l'essai sans justification, sans conséquence sur la suite de votre traitement ni sur la qualité des soins qui vous seront fournir et sans conséquence sur la relation avec votre médecin ; vous pourrez être suivi par la même équipe médicale.

Le promoteur de cette étude, qui en assure la gestion et la responsabilité, est l'Institut Bergonié, Centre régional de Lutte Contre le Cancer du Sud-Ouest situé au 229, cours de l'Argonne, 33076 Bordeaux cedex.

Conformément aux dispositions de la loi relative à l'informatique, aux fichiers et aux libertés, vous disposez à tout moment d'un droit d'accès et de rectification des données informatisées vous concernant (loi n° 2004-801 du 6 août 2004 modifiant la loi n° 78-17 du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés). Vous disposez également d'un droit d'opposition à la transmission des données couvertes par le secret professionnel susceptibles d'être utilisées dans le cadre de cette recherche et d'être traitées. Vous pouvez également accéder directement ou par l'intermédiaire du médecin de votre choix à l'ensemble de vos données médicales en application des dispositions de l'article L1111-7 du code de la santé publique. Ces droits s'exercent auprès du médecin qui vous suit dans le cadre de la recherche et qui connaît votre identité.
Conformément à la loi n°2004-806 du 9 août 2004 relative à la Politique de Santé Publique (art L1121-1 à L1126-6 du code de la santé publique) :

- cette recherche a obtenu un avis favorable du Comité de Protection des Personnes du Sud-Ouest et Outre-Mer III le 30/10/2013 et l'autorisation de l'Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM) le 13/11/2013,
- le promoteur de cette recherche, l'Institut Bergonié (Centre régional de Lutte Contre le Cancer du Sud-Ouest situé au 229, cours de l'Argonne, 33076 Bordeaux cedex), a souscrit une assurance de responsabilité civile auprès de HDI GERLING, TOUR OPUS 12, 77, Esplanade de la Défense 92914 Paris LA DEFENSE, n° police 0100871914011-130002-10998,
- les personnes ayant subi un préjudice après participation à une recherche biomédicale peuvent faire valoir leurs droits auprès des commissions régionales de conciliation et d'indemnisation des accidents médicaux,
- lorsque cette recherche sera terminée, vous serez tenus informés personnellement des résultats globaux par votre médecin dès que ceux-ci seront disponibles, si vous le souhaitez.

L'Institut Bergonié a pris toutes les dispositions prévues par la loi relative à la protection des personnes se prêtant à des recherches biomédicales, loi Huriet (n°88-1138) du 20 décembre 1988 modifiée par la loi de santé publique (n°2004-806) du 9 août 2004 et le décret d'application n°2006-477 du 26 avril 2006 relatif aux recherches biomédicales.

Le Docteur …… (Tél. ……..) se tient à votre disposition pour répondre à toutes vos éventuelles questions complémentaires.

Dr.....Tél.....

Formulaire de recueil de consentement(1) destiné aux personnes participant au protocole de Recherche Biomédicale « *CYCLIGIST* »

Etudes biologiques optionnelles

Titre de l'essai : Efficacité et tolérance du PD-0332991 chez les patients atteints d'une Tumeur Stromale Gastro-intestinale (GIST) localement avancé, réfractaire à Imatinib et Sunitinib : essai de phase 2

(1) Un exemplaire co-signé doit être remis à la personne qui participe à la recherche et à l'investigateur

Promoteur : Institut Bergonié, 229 Cours de l'Argonne, 33076 BORDEAUX Cedex.

Investigateur Coordonnateur : Dr Antoine ITALIANO, Département d'Oncologie Médicale, Institut Bergonié, 229 Cours de l'Argonne, 33076 BORDEAUX Cedex.

Je soussigné(e).....*(nom, prénom)* certifie avoir lu et compris la note d'information qui m'a été remise.

J'ai eu la possibilité de poser toutes les questions que je souhaitais au Pr/Dr……. *(nom, prénom)* qui m'a expliqué la nature, les objectifs, les risques potentiels et les contraintes liées à ma participation à cette recherche.

Je connais la possibilité qui m'est réservée d'interrompre ma participation à cette recherche à tout moment sans avoir à justifier ma décision et je ferai mon possible pour en informer le médecin qui me suit dans la recherche. Cela ne remettra naturellement pas en cause la qualité des soins ultérieurs.

J'ai eu l'assurance que les décisions qui s'imposent pour ma santé seront prises à tout moment, conformément à l'état actuel des connaissances médicales.

Je suis informé(e) que la possibilité qu'une partie des prélèvements effectués à l'occasion de ce protocole de recherche soit conservée pour une utilisation ultérieure à des fins de recherche. J'ai également été informé(e) de mon droit à m'opposer à ce que cette conservation et cette utilisation ultérieure à des fins de recherche aient lieu.

J'ai pris connaissance que cette recherche a reçu l'avis favorable du Comité de Protection des Personnes du Sud-Ouest et Outre-Mer III le 30/10/2013 et l'autorisation de l'ANSM le 13/11/2013 et a fait l'objet d'une déclaration à la Commission Nationale Informatique et Libertés (CNIL).

Le promoteur de la recherche l'Institut Bergonié (Centre régional de Lutte Contre le Cancer du Sud-Ouest situé au 229, cours de l'Argonne, 33076 Bordeaux cedex) a souscrit une assurance de responsabilité civile en cas de préjudice auprès de la société HDI GERLING, TOUR OPUS 12, 77, Esplanade de la Défense 92914 Paris LA DEFENSE, n° police 0100871914011-130002-10998.

J'accepte que les personnes qui collaborent à cette recherche ou qui sont mandatées par le promoteur, ainsi qu'éventuellement le représentant des Autorités de Santé, aient accès à l'information dans le respect le plus strict de la confidentialité.

J'accepte que les données enregistrées à l'occasion de cette recherche puissent faire l'objet d'un traitement informatisé sous la responsabilité du promoteur.

J'ai bien noté que, conformément aux dispositions de la loi relative à l'informatique, aux fichiers et aux libertés, je dispose d'un droit d'accès et de rectification. Je dispose également d'un droit d'opposition à la transmission des données couvertes par le secret professionnel susceptibles d'être utilisées dans le cadre de cette recherche et d'être traitées. Ces droits s'exercent auprès du médecin qui me suit dans le cadre de cette recherche et qui connaît mon identité.

Mon consentement ne décharge en rien l'investigateur et le promoteur de la recherche de leurs responsabilités à mon égard. Je conserve tous les droits garantis par la loi.

Les résultats globaux de la recherche me seront communiqués directement, si je le souhaite, conformément à la loi du 4 mars 2002 relative aux droits des malades et à la qualité du système de santé.

Ayant disposé d'un temps de réflexion suffisant avant de prendre ma décision, j'accepte librement et volontairement de participer à la sous-étude Cycligist /__/ ***oui*** /__/ ***non***

Je pourrai à tout moment demander des informations complémentaires au médecin qui m'a proposé de participer à cette recherche, n° téléphone :

Fait à _____ Fait à _____

Le └┘└┘ └┘└┘ └┘└┘└┘└┘ Le └┘└┘ └┘└┘ └┘└┘└┘└┘

Signature du patient : **Signature du médecin :**

APPENDIX 16: PATHOLOGY EXPERT CENTERS IN SARCOMA

	Sites	Structures anapath	Spécificité
Site Coordonnateur Institut Bergonié	Institut Bergonié	Département de Pathologie	tout sarcome
	Hôpital Pellegrin Bordeaux	Service d'anatomie pathologique	tout sarcome
	Hôpital Haut-Lévèque Pessac	Service d'anatomie pathologique	tout sarcome
Site Coordonnateur Centre Léon Bérard	Centre Léon Bérard	Département d'anatomie pathologique	tout sarcome
	Hôpital Edouard Herriot	Laboratoire d'anatomie pathologique	GIST*
	Hôpital de la Croix Rousse	Service d'anatomie pathologique	gynécopathologie**
Site Coordonnateur Institut Gustave Roussy	Institut Gustave Roussy	Service de Pathologie Morphologique	tout sarcome
CRE AP-HP Ile de France	Hôpital Ambroise Paré	Service d'anatomie pathologique	GIST*
	Hôpital Cochin	Service d'anatomie pathologique	tout sarcome
	Hôpital Pitié-Salpétrière	Service d'anatomie pathologique	tout sarcome
	Hôpital Saint-Antoine	Service d'anatomie pathologique	tout sarcome
	Hôpital Saint-Louis	Service d'anatomie pathologique	sarcomes cutanés***
	Hôpital Bichat - Claude Bernard	Service d'anatomie pathologique	tout sarcome
	Hôpital Henri Mondor	Service d'anatomie pathologique	sarcomes cutanés***
	CHU d'Amiens	Service d'anatomie pathologique	gynécopathologie**
CRE Institut Curie	Institut Curie	Service de Pathologie	tout sarcome
CRE Strasbourg	Centre Paul Strauss	Service d'anatomie pathologique	tout sarcome
	Hôpital de Hautepierre	Département de Pathologie	tout sarcome
	Hôpital Civil	Laboratoire d'histopathologie cutanée	sarcomes cutanés***
CRE Clermont Ferrand	Centre Jean Perrin	Service d'anatomie pathologique	tout sarcome
	Hôpital Gabriel Montpied	Service de Pathologie	tout sarcome
CRE Caen	CHRU de Caen	Service d'anatomie pathologique	tout sarcome
	Centre François Baclesse	Service d'anatomie pathologique	tout sarcome
CRE Dijon	Centre Georges François Leclerc	Service d'anatomie pathologique	tout sarcome
	CHRU de Dijon	Service d'anatomie pathologique	GIST*
	CHRU de Besançon	Service d'anatomie pathologique	tout sarcome

CRE Rennes	Hôpital Pontchaillou	Service d'anatomie pathologique	tout sarcome
CRE Tours	Hôpital Trousseau	Service d'anatomie pathologique	tout sarcome
CRE Brest	Hôpital Morvan	Service d'anatomie pathologique	tout sarcome
CRE Rouen	Hôpital Charles Nicolle	Service d'anatomie pathologique	tout sarcome
	Centre Henri Becquerel	Service d'anatomie pathologique	tout sarcome
CRE Montpellier	Centre Val d'Aurelle	Service d'anatomie pathologique	tout sarcome
	Hôpital Gui de Chauliac	Laboratoire d'anatomie pathologique	tout sarcome
CRE Limoges	Hôpital Dupuytren	Laboratoire de Pathologie	tout sarcome
CRE Nancy	Centre Alexis Vautrin	Service d'anatomie pathologique	tout sarcome
	Hôpital Central de Nancy	Laboratoire d'anatomie pathologique	tout sarcome
CRE Toulouse	Institut Claudius Regaud	Service d'anatomie pathologique	tout sarcome
	Hôpital Rangueil	Service d'anatomie pathologique	tout sarcome
	Hôpital Purpan	Laboratoire d'anatomie pathologique	GIST*
CRE Lille	Centre Oscar Lambret	Laboratoire d'anatomie pathologique	tout sarcome
	CHRU de Lille	Centre de Biologie Pathologie	tout sarcome
CRE Nantes	Hôtel Dieu	Service d'anatomie pathologique	tout sarcome
CRE Angers	Centre Paul papin	Service d'anatomie pathologique	tout sarcome
	CHRU d'Angers	Département de Pathologie	tout sarcome
CRE Marseille	Institut Paoli Calmettes	Département de Bio-Pathologie	tout sarcome
	Hôpital La Timone	Service d'anatomie pathologique	tout sarcome
	Hôpital Nord Marseille	Laboratoire d'anatomie pathologique	gynécopathologie**
CRE Nice	Centre Antoine Lacassagne	Unité d'anatomie pathologique	tout sarcome
	Hôpital Pasteur	Laboratoire d'anatomie pathologique	tout sarcome

GIST* : structure ne pouvant relire que des GIST
Gynécopathologie** : structure ne pouvant relire que des sarcomes de la sphère gynécologique
Sarcomes cutanés*** : structure ne pouvant relire que des sarcomes cutanés

APPENDIX 17: PATIENT DIARY

PROTOCOLE

CYCLIGIST

Carnet patient

De Mme/Mr.....

Cycle N° |__|__|

Madame, Monsieur,

Dans le cadre de votre participation à l'étude Cycligist, il est nécessaire d'avoir des informations sur le suivi de votre traitement par **PD-0332991**

Vous trouverez dans ce carnet un tableau à compléter chaque jour, et nous vous remercions d'y noter :

- ✓ la date, et le nombre de gélules pris par jour
- ✓ d'annoter un commentaire si nécessaire (effets secondaires par exemple)
- ✓ l'indication de non prise du **PD-0332991** s'il y a lieu en cochant la case correspondante et en complétant d'un commentaire la raison.

N'oubliez pas de remettre ce livret à l'Infirmièr(e) de Recherche Clinique, Attaché(e) de Recherche Clinique ou Pharmacie hospitalière lors de votre prochain rendez-vous.

Nous vous remercions de votre précieuse collaboration.

Notice d'utilisation du médicament à l'étude

- ✓ 1 prise par jour à heure fixe
- ✓ au moins une heure avant ou deux heures après un repas
- ✓ à prendre avec un grand verre d'eau

En cas d'oubli

- Ne pas prendre la dose, et ne pas doubler la dose suivante

En cas de vomissements

- Ne pas reprendre la dose, et ne pas doubler la dose suivante

Conservation du traitement

- ○ Conservation à température ambiante inférieure à 30°C.
- ○ Ne pas utiliser après la date de péremption figurant sur la boite

Tenir hors de portée des enfants

	Date	PD-0332991 Nombre de gélules		Non pris	Commentaires
J1	___/___/___	|__|gél de ___mg	|__|gél de ___mg	☐	
J2	___/___/___	|__|gél de ___mg	|__|gél de ___mg	☐	
J3	___/___/___	|__|gél de ___mg	|__|gél de ___mg	☐	
J4	___/___/___	|__|gél de ___mg	|__|gél de ___mg	☐	
J5	___/___/___	|__|gél de ___mg	|__|gél de ___mg	☐	
J6	___/___/___	|__|gél de ___mg	|__|gél de ___mg	☐	
J7	___/___/___	|__|gél de ___mg	|__|gél de ___mg	☐	
J8	___/___/___	|__|gél de ___mg	|__|gél de ___mg	☐	
J9	___/___/___	|__|gél de ___mg	|__|gél de ___mg	☐	
J10	___/___/___	|__|gél de ___mg	|__|gél de ___mg	☐	
J11	___/___/___	|__|gél de ___mg	|__|gél de ___mg	☐	
J12	___/___/___	|__|gél de ___mg	|__|gél de ___mg	☐	
J13	___/___/___	|__|gél de ___mg	|__|gél de ___mg	☐	
J14	___/___/___	|__|gél de ___mg	|__|gél de ___mg	☐	
J15	___/___/___	|__|gél de ___mg	|__|gél de ___mg	☐	
J16	___/___/___	|__|gél de ___mg	|__|gél de ___mg	☐	
J17	___/___/___	|__|gél de ___mg	|__|gél de ___mg	☐	
J18	___/___/___	|__|gél de ___mg	|__|gél de ___mg	☐	
J19	___/___/___	|__|gél de ___mg	|__|gél de ___mg	☐	
J20	___/___/___	|__|gél de ___mg	|__|gél de ___mg	☐	
J21	___/___/___	|__|gél de ___mg	|__|gél de ___mg	☐	
J22	Pas de traitement				
J23	Pas de traitement				
J24	Pas de traitement				
J25	Pas de traitement				
J26	Pas de traitement				
J27	Pas de traitement				
J28	Pas de traitement				