Protocol PONALLO

Version 1.1 du 19/03/2018

Eudract: No. 2017-004282-28
Ref: CHV P17/01

"Phase 2 study of Ponatinib (Iclusig) for prevention of relapse after allogeneic stem cell transplantation (allo-SCT) in FLT3-ITD AML patients: the PONALLO trial.**"**

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SIGNATURE PAGE

SPONSOR SIGNATURE

The sponsor agrees to comply with the laws and regulations on clinical trials for the conduct of the above-mentioned study and agrees to abide by all provisions set forth therein.		
Name and capacity of the signatory representative:	**Date:**	**Signature:**

INVESTIGATOR'S SIGNATURE

I have read all the pages of the clinical trial protocol sponsored by Nantes University Hospital. I confirm that this protocol contains all the information necessary for the conduct of the trial. I agree to conduct the trial according to the protocol and to abide by all provisions set forth therein. I agree to conduct the trial in compliance with:

- the principles of the "Declaration of Helsinki",
- international (ICH) and French good clinical practice regulations and guidelines (Règles de bonnes pratiques cliniques pour les recherches biomédicales portant sur des médicaments à usage humain (Décision du 24 novembre 2006))
- national laws and regulations relating to clinical trials,
- the current European Clinical Trials Directive

I also agree for the investigators and other qualified members of my staff to have access to the copies of this protocol and documents concerning the conduct of the study so that they abide by all provisions set forth therein.

	Name:	**Date:**	**Signature:**
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Principal investigator	**Name and institution:**	**Date:**	**Signature:**

LIST OF ABBREVIATIONS

ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé
MA	Marketing Authorisation
CRA	Clinical Research Associate (monitor)
GCP	Good Clinical Practice
ERB	Ethical Review Board
CNIL	Commission Nationale de l'Informatique et des Libertés
CRF	Case Report Form
eCRF	Electronic Case Report Form
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
USAR	Unexpected Serious Adverse Reaction
RM	Reference Methodology
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
CRT	Clinical Research Technician

CONTENTS

INTRODUCTION AND ABSTRACT

Prognosis of AML patients harbouring FLT3-ITD mutations remain associated with a higher risk of relapse after allogeneic stem cell transplantation. Maintenance therapy is definitely needed to decrease incidence of relapse after transplant in these patients. Targeted therapies directed against FLT-3 have been developed these recent years showing encouraging results both in monotherapy or in combination with chemotherapy. Ponatinib is a third generation anti-Bcr-ABl tyrosine kinase inhibitor with anti-FLT3 property which may be of interest as maintenance treatment after transplant in AML FLT3-ITD patients.
Here we propose a Phase 2 study testing the efficacy and tolerability of ponatinib 30 mg/day from day+60 for one year post-transplant in such patients. 77 patients will be included with the main objective to demonstrate a lower incidence of relapse at 2 years (15%) compared to what it has been reported in the literature (around 30% of relapse post-transplant).

Introduction et Résumé

Les LAM avec mutation FLT3-ITD présentent un taux de rechute important même après allogreffe de cellules souches hématopoietiques (environ 30% à 2 ans). Un des moyens de diminuer le taux de rechute post-allogreffe chez ces patients est d'utiliser un traitement de maintenance anti-FLT3. En effet, un certain nombre de molécules anti-FLT3 sont disponibles aujourd'hui et ont montré une efficacité en monothérapie ou en association avec la chimiothérapie. Le ponatinib est un inhibiteur puissant anti-multikinase dont des propriétés anti-BcrAbl et anti-FLT3. Nous souhaitons ici tester dans le cadre d'une étude de Phase 2 le ponatinib à la dose de 30 mg/j en maintenance post-allogreffe chez des patients LAM FLT3-ITD mutés. Le traitement sera débuté dès le Jour+60. 77 patients seront inclus avec pour objectif de démontrer un moindre taux de rechute (15% à 2 ans) avec cette stratégie. Une étude de tolérance sera également associée à l'objectif principal.

1. JUSTIFICATION OF THE STUDY

1.1. POSITIONING OF THE STUDY

Acute Myeloid Leukemia (AML) in adults.
Acute myeloid leukemia (AML) is a heterogeneous disease with respect to presentation and clinical outcome, with a median age of presentation in the late 60s. In patients younger than 60 years, between 70% and 80% enter complete remission (CR) after one or two induction treatments leading to cure in approximately 40% of patients. Prognosis of adult patients with AML after first relapse remains very poor. Complete response rates range from 25% to 40%. Few patients survive after intensive chemotherapy with or without allogeneic hematopoietic stem cell transplant (HSCT).
Non-random chromosome abnormalities occur in 50% to 60% of patients. The prognostic relevance of cytogenetic abnormalities has led to the widespread adoption of risk stratification, with patients divided into three cytogenetically defined risk groups. The accumulation of molecular information provided powerful additional prognostic information. It has become clear that specific chromosome abnormalities and molecular genetic changes are among the most important prognostic markers and therefore may be used for stratification of AML patients to risk-adapted therapeutic strategies. Recently, FLT3, NPM1, and CEBPA mutational analysis was shown to improve risk stratification for patients who do not have karyotypic abnormalities (approximately 50% of AML patients).

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FLT3 genetic alterations in AML.
FLT3 encodes a Class III receptor tyrosine kinase that consists of 5 immunoglobulin-like domains, a transmembrane domain, a cytoplasmic juxtamembrane domain, and 2 tyrosine kinase domains. FLT3 is normally expressed on bone marrow hematopoietic stem cells, but this expression is lost as these cells differentiate. In coordination with other growth factors, FLT3 plays a crucial role in normal hematopoiesis and cellular growth in primitive hematopoietic stem and progenitor cells.
FLT3 is expressed on the leukemic cells in 70% to 100% of AML patients. Constitutively active mutant FLT3 results in the proliferation and survival of leukemic blasts. FLT3 genetic alterations include FLT3 somatic point mutations within the second tyrosine kinase domain and internal duplications of the juxtamembrane domain. This alteration is refered to as FLT3-ITD. The FLT3-ITD mutation is found in around 30% of the patients with cytogenetically normal AML. Patients with the FLT3-ITD genotype have been reported to have a poor outcome when treated with conventional chemotherapy with an estimated 4-year relapse-free survival of 25%. More recently, the prognostic relevance of FLT3-ITD has been studied in the context of integrated genetic profiling. This study confirmed the genetic complexity of AML and also confirmed that FLT3-ITD was associated with reduced overall survival in intermediate-risk AML. A multivariate analysis of several genetic alterations revealed that FLT3-ITD was the primary predictor of patient outcome. FLT3-ITD mutations were classified

in 3 categories: 1) FLT3-ITD with +8, TET2, DNMT3A or MLL-PTD mutations (3-year OS 14.5%); 2) FLT3-ITD with wild type CEBPA, TET2, DNMT3 and MLL-PTD (3-year OS 35.2%) and 3) FLT3-ITD with CEBPA mutations (3-year OS 42%). However, FLT3-ITD was not a predictor of response to induction therapy, allowing the introduction of targeted therapies after the induction course.

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FLT3 inhibition in AML.

Several FLT3 inhibitors have been evaluated or are currently tested in the setting of relapsing AML. In most trials patients were only eligible if the FLT3-ITD mutation was present. Disappointing results were reported with the first generation of FLT3 inhibitors, including lestaurtinib (CEP-701), midostaurin (PKC-412) and sorafenib. Second generation FLT3 inhibitors such as quizartinib (AC220) are currently under investigation with promising results. However, the hematologic toxicity of AC220 will probably represent a major limitation to evaluate it in combination with standard or high-dose chemotherapy.

Ponatinib (AP24534) is a third-generation tyrosine kinase inhibitor targeting the BCR-ABL tyrosine kinase domain. Ponatinib was rationally designed with an extensive network of optimized molecular contacts and triple bonds to accommodate the T315I mutation, a major cause of resistance to tyrosine kinase inhibitors in chronic and advanced phase chronic myelogenous leukemia (CML). Ponatinib also has in vitro inhibitory activity against a discrete set of kinases implicated in the pathogenesis of other hematologic malignancies, including FLT3, KIT, fibroblast growth factor receptor 1 (FGFR1), and platelet derived growth factor receptor α (PDGFRα) (O'Hare T, Cancer Cell 2009).

Ponatinib has been reported to have significant cellular activity against leukemic cell line which harbors a FLT3-ITD activating mutation. In the study by Gozgit et al (Mol Cancer Ther 2011), in MV4-11 (FLT3-ITD(+/+)) but not RS4;11 (FLT3-ITD(-/-)) AML cells, ponatinib inhibited FLT3 signaling and induced apoptosis at concentrations of less than 10 nmol/L. In an MV4-11 mouse xenograft model, once daily oral dosing of ponatinib led to a dose-dependent inhibition of signaling and tumor regression. Ponatinib inhibited viability of primary leukemic blasts from a FLT3-ITD positive AML patient (IC50 4 nmol/L) but not those isolated from 3 patients with AML expressing native FLT3. Overall, these results support the investigation of ponatinib in patients with FLT3-ITD-driven AML and other hematologic malignancies driven by KIT, FGFR1, or PDGFRα.

The treatment with ponatinib for FLT3-mutant AML may also decrease the secondary resistance rates due to FLT3-TKD mutations (Zirm et al, BJH 2012).

Finally, Shah et al analyzed the results of 12 patients with AML who were treated in the phase I trial of ponatinib at the dose of 45 mg po daily. The median age of the patients was 49 years (range, 30-72) and they were all heavily pre-treated (median number of prior therapies 3, range 1-7). FLT3-ITD was present in 7/12 patients (58%). Nine patients had one or more treatment-related adverse event with the most commonly noted toxicity being pancreatitis (3 patients, all grade 2). The overall response rate was 25% (3/12 patients), with

2 CRi and 1 PR. All 3 were noted to have FLT3-ITD mutations. The authors concluded that ponatinib should be considered for further testing as a FLT3 kinase inhibitor in AML. (Shah et al; BJH 2013).

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FLT3 + AML and allograft

Patients presenting with FLT3+ AML are referred for early allogeneic stem-cell transplantation (allo-SCT). However, some data suggest that FLT3-ITD remains associated with a poor prognosis even after allo-SCT because of higher risk of relapse and strategies for preventing relapse in the post-transplant setting are required (Hu et al, Expert Rev Hematol, 2014). For example, in a large cohort of patients (Brunet et al, JCO, 2012), the incidence of relapse for FLT3-ITD AML patients after allo-SCT was 30% at 2-years, significantly higher compared to FLT3-ITD negative patients (p=0.006). Few anti-FLT3 inhibitors, such as quizartinib (or AC220) or sorafenib have been tested after allotransplant, either in relapse or as a maintenance therapy. For example, sorafenib is a pan-kinase inhibitor, including FLT3, which has been tested after allotransplant as a maintenance agent for preventing relapse of FLT3-ITD+ AML patients showing very encouraging results (Chen et al, BBMT 2014; Tarlock et al, PBC 2015; Brunner et al, BJH 2016; Battipaglia et al, Cancer 2017; Sandmaier et al, AJH 2018). As the majority of relapse occurs within 1 year post-transplant and that the majority of studies showed that the median duration of the maintenance is one year, it seems that there is no rational to pursue anti-FLT3 inhibitors over this period.

Ponatinib is also a multikinase inhibitor, including FLT3, which can be of high interest as it is active against clinically relevant FLT3-ITD mutant isoforms that confer resistance to quizartinib or sorafenib (Smith et al, Blood 2013). No study is dedicated to the use of ponatinib in the post-transplant setting in order to prevent relapse in these patients.

The main objective of this study will be to demonstrate a better in FLT3-IDT+ AML adults receiving ponatinib as post-transplant maintenance.

The study is to be sponsored by CH de Versailles and supported by Incyte inc. Indeed, Incyte et al will provides ponatinib and financial support for the study.

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1.2. BENEFITS AND RISKS FOR SUBJECTS TAKING PART IN THE STUDY

1.2.1. Benefits

1.2.1.1. Individual benefit

The prognosis of FLT3+ AML patients is associated with higher risk of relapse after allogeneic transplantation. One can expect a decrease in terms of relapse incidence and an improvement of OS by administering ponatinib after transplant in this population which may translate into an individual benefit for each patient.

1.2.1.2. Collective benefit

By reducing relapse and improving OS in allotransplanted FLT3+ AML patients one can expect less hospitalizations, transfusions and overall a cost-effectiveness treatment using ponatinib post-transplant.

1.2.2. Risks

1.2.2.1. Individual risk

- Physical risks and constraints

The physical risks are represented by additional days of hospitalization, consultations and travels, all along the treatment, then in case of adverse events.

- Disease-related risks

This could be aplasia, infections, haemorrhage, metabolic disorders, compressive tumour, central nervous system leukemic invasion, relapse and deaths.

- Test treatment risks including comparator if applicable (adverse reactions)

Ponatinib may be responsible for: anemia, leucopenia, thrombopenia, cardiac vascular, peripheral vascular, and cerebrovascular arterial occlusive events, venous thromboembolic events, QT prolongation and torsade de pointe.
The most common all-grade adverse events include hypertension, rash, abdominal pain, fatigue, headache, arterial ischemia, dry skin, constipation, arthralgia, nausea, pyrexia, peripheral neuropathy, myalgia, pain in extremity, back pain, diarrhea and pancreatitis.

- Associated treatment-related risks

These are risks associated with medication administered after allotransplant in patients:

Ciclosporine: infections, nephrotoxicity (impaired renal function), thrombotic microangiopathy, hyperkaliema, hepatotoxicity (cholestasis, jaundice, hepatitis, and liver failure), secondary malignancies (lymphoma, skin), neurotoxicity (Posterior Reversible Encephalopathy Syndrome (PRES), impaired consciousness, convulsions, visual disturbances (including blindness), loss of motor function, movement disorders and psychiatric disturbances).

Mycophenolate mofetyl: diarrhea, nausea, vomiting, joint pain; infections, leukopenia, and/or anemia, fatigue, headache, cough and/or breathing issues, esophagitis, gastritis, gastrointestinal tract haemorrhage. More rarely: pulmonary fibrosis or various neoplasia (melanoma, lymphoma, other malignancies), pure red cell aplasia (PRCA).

Corticosteroids (for GVHD treatment): infections, neuropsychiatric (steroid psychosis, anxiety, depression), diabetes mellitus, hypocalcemia, hypokalaemia, hypertension, Cushing syndrome, colitis and peptic ulceration, cataract and retinopathy,

Posaconazole, as fungal prophylaxis in case of GVHD: fever, diarrhea, nausea, vomiting, and headache. Other notable adverse events included hypokalemia, rash, thrombocytopenia, and abdominal pain. Less frequent: elevated liver enzyme levels, hyperbilirubinemia, and hepatocellular damage, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, pulmonary embolus, adrenal insufficiency, and allergic and/or hypersensitivity reactions, prolongation of the QT interval.

- Psychological risks and constraints

Psychological constraints directly associated with disease or resulting from the study are distress, feeling of dependence, fear for the future of the treatment at the end of the study, depression.

- Socio-economic risks

Not applicable

1.2.2.2. Collective risk

Not applicable

1.2.3. Benefit / risk balance

Prognosis of allotransplanted FLT3+ AML patients is associated with a higher risk of relapse after allogeneic transplantation. Maintenance therapy with ponatinib post-transplant may help to improve outcomes in this population. Ponatinib has been already tested in monotherapy or in association with chemotherapy showing a safety profile and very encouraging results, justifying its use in allotransplanted FLT3+ AML patients.

1.3. DESCRIPTION AND JUSTIFICATION OF THE TREATMENT PLAN

In this study, ponatinib will be administered from day+60 post-transplant during one year in FLT3+ AML patients. Flt3+ AML are at high risk of relapse and the median time of relapse is 5/6 months: we must act early to prevent relapse in such patients.

In our study, an intermediate dose of ponatinib (30 mg/day) will be used. This was retained in order: 1) to minimize potential toxicities, including liver and cardiac disorders and prolonged thrombocytopenia; and 2) to allow delivery of standard drugs used after allotransplant.

2. OBJECTIVES AND ENDPOINTS

2.1. PRIMARY OBJECTIVE AND ENDPOINT

2.1.1. Primary objective

Relapse incidence at 2 years

2.1.2. Primary endpoint

Relapse is defined by the reoccurrence of AML disease, either in bone marrow with morphologically >=5% of blasts or presence of extramedullary disease (granulocytic sarcoma).

2.2. SECONDARY OBJECTIVES AND ENDPOINTS

2.2.1. Secondary objective(s)

- Overall survival (OS) at 2 years
- Leukemia-free survival (LFS) at 2 years
- Non-relapse mortality (NRM) at day+100, 1-year and 2-year
- Acute and chronic GVHD
- T, B and NK cell reconstitutions at +3, +6, +9 and +12 months post-transplant
- Chimerism at day 30, 60, 90, +6, +12 months post-transplant
- Rate of patients who will stop ponatinib during the first year of transplant and reasons for stopping ponatinib (relapse, toxicity, other…)
- To evaluate safety
- To evaluate minimal residual disease (MRD): before graft and at each myelogram performed after allograft

2.2.2. Secondary endpoint(s)

- Overall survival: time interval from the graft (day 0) until the date of last follow-up or death
- Leukemia free survival: time interval from the date of the graft (day 0) until the date of last follow-up, death or relapse
- Non relapse mortality: incidence of mortality due to all causes except relapse after transplant, considering that cause of death for patients having relapsed but dying from another cause is relapse.
- GVHD: NIH score

- Immune reconstitution: flow cytometry
- Chimerism: RT-PCR
- Toxicity: (NCI CTC version 4)

MRD: flow cytometry (Lacombe F, Campos L, Allou K et al. Prognostic value of multicenter flow cytometry harmonized assessment of minimal residual disease in acute myeloblastic leukemia. Hematol Oncol. 2017 Dec 7. doi: 10.1002/hon.2488. [Epub ahead of print]

2.3. OBJECTIVE AND ENDPOINTS FOR ANCILLARY STUDIES

Not applicable

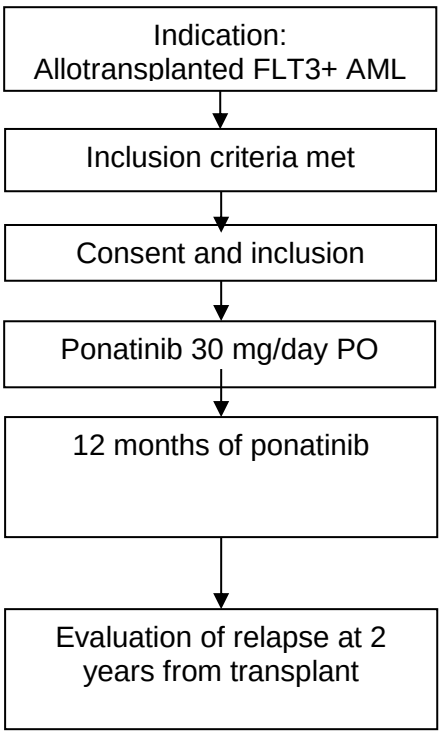
3. STUDY DESIGN

3.1. GENERAL STUDY METHODOLOGY

The study presents the following characteristics:

- **Phase 2 study** (drug, clinical)
- **Multi-centre** (national)
- **Not Controlled**
- **Not Randomised**
- **Open**
- **Prospective**

3.2. STUDY DIAGRAM



4. STUDY POPULATION

4.1. DESCRIPTION OF THE POPULATION

Positive FLT-3 ITD AML

4.2. PRE-INCLUSION CRITERIA

These criteria will be checked within one-month pre-transplant

- Patient affiliated to or beneficiary of the French National Health Service
- Having or not received previously ponatinib
- Age ≥ 18 and ≤ 70
- With Positive FLT-3 ITD AML and eligible for an allo-SCT (myeloablative, sequential or reduced-intensity)
- Any type of donor without contra-indication for stem cell mobilization

4.3. INCLUSION CRITERIA

These criteria will be checked between days + 30 and day 60 post-transplant.

Patients with
- Engraftment
- Controlled GVHD
- Positive FLT-3 ITD AML in cytologic complete remission
- Have an Eastern Cooperative Oncology Group (ECOG) performance status < 2 (**ANNEXE 5**)
- Have adequate renal function: Serum creatinine ≤ 1.5 × upper limit of normal (ULN) for institution
- Have adequate hepatic function: Total serum bilirubin ≤ 1.5 × ULN, unless due to Gilbert's syndrome; Alanine aminotransferase (ALT) ≤ 2.5 × ULN, or ≤ 5 × ULN if leukemic infiltration of the liver is present ; Aspartate aminotransferase (AST) ≤ 2.5 × ULN, or ≤ 5 × ULN if leukemic infiltration of the liver is present
- Have normal pancreatic status: Serum lipase and amylase ≤ 1.5 × ULN
- Have normal QTcF interval on screening electrocardiogram (ECG) evaluation,defined as QTcF of ≤ 450 ms in males or ≤ 470 ms in females.
- Platelets ≥ 100 Giga/l; Neutrophils ≥ 1 Giga/l
- Have a negative pregnancy test documented prior to enrollment (for females of childbearing potential).
- Agree to use an effective form of contraception with sexual partners throughout study participation (for female and male patients who are fertile).
- Provide written informed consent.
- Be willing and able to comply with scheduled visits and study procedures.

Patients who do not fulfil these criteria will be excluded from the study and replaced one by one.

4.4. EXCLUSION CRITERIA

These criteria will be checked one month pre-transplant:

- HIV positive, active Hepatitis B or C
- Childbearing or childbreast feading women
- Women or men without effective contraceptive barrier if needed
- Previous myocardial infarction, or cerebral vascular accident, pancreatitis
- Respiratory insufficiency defined as DLCO <40% of the corrected value
- Creatinine clearance ≤ 50ml/min
- Contra-indication to ponatinib
- Previous or concurrent second malignancy except for adequately treated basal cell carcinoma of the skin, curatively treated in situ carcinoma of the cervix, curatively treated solid cancer, with no evidence of disease for at least 2 years
- Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule

- Patients at high or very high risk of cardiovascular disease with any of the following
  a) Established cardiovascular disease Cardiac disease:
    - Congestive heart failure greater than class II NYHA or
    - Left ventricular ejection fraction (LVEF) < 50% or
    - Unstable angina (anginal symptoms at rest) or
    - New onset angina (began within the last 3 months) or
    - Myocardial infarction, coronary/peripheral artery disease, congestive heart failure, cerebrovascular accident including transient ischemic attack within the past 12 months or
    - History of thrombolic or embolic events Arrhythmias
    - Any history of clinically significant cardiac arrhythmias requiring anti-arrhythmic therapy.
  b) Diabetes Mellitus,
  c) Arterial Hypertension,
    - Uncontrolled hypertension defined as systolic blood pressure greater than 140 mmHg or diastolic pressure greater than 90 mmHg, despite optimal medical management and optimal measurement (http://www.has-sante.fr/portail/display.jsp?id=c_272459)
    - Any history of hypertension with
      - Hypertensive encephalopathy
      - Posterior leucoencephalopathy
      - Aortic or artery dissection
  d) Familial dysplipidemia.
  e) Taking medications that are known to be associated with Torsades de Pointes (see **ANNEXE 6)**

5. STUDY TREATMENTS

5.1. DESCRIPTION AND MODE OF ADMINISTRATION

5.1.1. Study treatment(s)

5.1.1.1. Treatments

Iclusig: (PONATINIB)

Molecule name: Iclusig 15, 30 mg film-coated tablets

Qualitative and quantitative product composition:
Each film-coated tablet contains 15 or 30 mg of ponatinib (as hydrochloride).
Excipients with known effect: each film-coated tablet contains 40 mg of lactose monohydrate.

Manufacturer of the molecule and/or holder of the marketing authorisation (MA): Incyte Biosciences France

AMM EU/1/13/839/005 ; CIP 3400930020029 (2015, RCP rév 26.01.2017) cp à 15 mg.

EU/1/13/839/006 ; CIP 3400930047613 (2015, RCP rév 26.01.2017) cp à 30 mg.

Pharmaceutical form and packaging used: *Film-coated tablet (tablet). White, biconvex, round film-coated tablet that is approximately 6 mm in diameter, with "A5" debossed on one side.*
There is no generic for Iclusig.

Mode of administration (route of administration, dosage, duration of treatment):
Therapy should be initiated by a physician experienced in the diagnosis and treatment of patients with leukaemia. Haematologic support such as platelet transfusion and haematopoietic growth factors can be used during treatment if clinically indicated.
Before starting treatment with ponatinib, the cardiovascular status of the patient should be assessed,including history and physical examination, and cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored and medical and supportive therapy for conditions that contribute to cardiovascular risk should be optimized during treatment with iclusig.
Posology
The recommended starting dose will be 30 mg of ponatinib once daily. For the standard dose of 30 mg once daily, a 30 mg film-coated tablet is available. Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity for a total period of 12 months.

5.1.1.2. Administration

Ponatinib administration will start for all patients at day+60 (if engraftment and complete remission confirmed and if GVHD, only if GVHD is controlled)
77 patients will receive ponatinib at a dose of 30 mg/day for 1-year.
After 1 year ponatinib is stopped and it is not allowed to start a new TKI or pursue ponatinib.

5.1.1.3. Dose adjustment

The dose of ponatinib will be adjusted according to toxicity with possibility to reduce the dose at 15 mg/day when toxicities due to this drug will be resolved.

*See **ANNEXE 4***

5.1.1.4. Reference documents

See: Investigator brochure

5.1.2. Other study treatments

5.1.2.1. Associated treatments

Standard treatments required in the context of allograft are allowed: ciclosporine A, mycophenolate mofetyl, amoxiciline, aciclovir and valaciclovir, corticosteroids, sulfamethoxazone-trimethoprime, posaconazole, voriconazole fluconazole.

5.1.2.2. Administration

At the discretion of the physician and according to center practice.

5.1.2.3. Dose adjustment

At the discretion of the physician and according to center practice.

5.2. AUTHORISED AND UNAUTHORISED TREATMENTS

5.2.1. Authorised treatments

Rhu-EPO is allowed in the event of symptomatic anemia (or Hb<10 g/dL) during maintenance
Rhu-GCSF is allowed during the maintenance phase in the event of neutropenia < 500/mm3.

5.2.2. Restricted treatments

To be avoided:
Agents able to increase ponatinib Cmax
Ketoconazole, itraconazole, ritonavir, clarithromycin, telithromycin, erythromycin, verapamil, diltiazem, amprenavir, fosamprenavir.

Posaconazole, voriconazole fluconazole and cyclosporine are allowed but closed surveillance of the patient is needed to avoid too much toxicity.

Agents susceptible to prolong QTc and Drugs with Risk of Torsade de Pointes
See **ANNEXE 6**.

To be used with caution:
Agents able to decrease ponatinib Cmax
Grapefruit juice, orange juice, caulophyllum, phytoestrogens, carbamazepine, phenobarbital, phenytoin, efavirenz, nevirapine, hypericum perforatum (millepertuis).

Particular caution:
Ponatinib therapy may induce elevations of pancreatic enzyme levels. If this occurs, it is recommended that a CT scan be performed. In the event of pancreatitis grade 2-3, ponatinib should be interrupted until the toxicity decreases to ≤ grade 1. In case of pancreatitis grade 4, ponatinib will not be resumed (DLT) (see **ANNEXE 4**).
Ponatinib therapy could induce QTc prolongation. In case of recurrent QTc prologation grade 3, consider DLT in the absence of recovery. In case of QTc grade 4, Ponatinib will not be resumed (DLT) (see **ANNEXE 4** for the clinical management of the patients).
Female and male patients who are of childbearing potential must agree to use an effective form of contraception with their sexual partners throughout participation in this study.
Ponatinib therapy may induce cardiovascular events. If this occurs, ponatinib will be discontinued and will not be resumed (see **ANNEXE 4**).

5.2.3. Emergency treatments (if applicable)

In case of anaphylactic reaction, adrenaline, antihistaminic, paracetamol/acetaminophen or corticosteroid should be immediately available.

5.3. TREATMENT COMPLIANCE FOLLOW-UP

Ponatinib will be delivered each month by the Pharmacy department of each center and patients should return the drug box for verifying/counting open and empty drugs to assess compliance to the treatment.

5.4. EXPERIMENTAL DRUG CIRCUIT

5.4.1. General circuit

The investigator will be responsible for providing ponatinib. Thus, it will be an in-house dispensary. Distribution will be supplied by the Pharmacy department of each center. Ponatinib will be relabeled to indicate that the drugs are used as part of the protocol.

5.4.2. Experimental drug storage conditions

5.4.2.1. Description of dispensary storage

Ponatinib:
Conservation: closed vial, away from direct sunlight. There is a dehydrate capsule that must stay inside the flask.

5.4.2.2. Description of department storage

At the study site, ponatinib must be stored in a locked, safe area to prevent unauthorized access. Also the study medication should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

5.4.2.3. Description of storage at patient's home

No particular precaution for conservation. The study medication should be stored at room temperature away from direct sunlight and protected from excessive heat and cold. Patient should be advised to not swallow the dehydrate capsule found in the flask.

5.4.3. Unblinding procedure

Not applicable

6. CONDUCT OF THE STUDY

6.1. TESTS AND ANALYSIS

6.1.1. Detailed description of the parameters for evaluating efficacy

Primary objective is relapse incidence at 2 years from transplant.
Parameters for evaluating relapse incidence will be:
-CBC (hemoglobin, hematocrit, RBC count, WBC count, differential leukocyte count, platelet count),
-Bone marrow aspiration with the documentation of relapse
-All exams needed to document extramedullary relapse: scan, pet-scan, biopsy, ect…

6.1.2. Description of tests and analysis

Conventional biological tests are similar to the standard follow-up used in each center for acute leukemia patients. The recommended schedule is shown in 6.2.

- Medical history
- Concomitant therapies
- ECOG performance status
- Physical examination, including weight, height, vital signs, cardiopulmonary examination and detailed evaluation of lymph nodes, liver and spleen
- 12-lead ECG and QTc calculation
- LVEF measurement by echocardiography
- Chest X-ray
- Laboratory assessments
    - Standard hematology tests including CBC (hemoglobin, hematocrit, RBC count, WBC count, differential leukocyte count, platelet count), prothrombin time, white cell morphology
    - Blood chemistry: including total bilirubin, AST, ALT, alkaline phosphatase, serum creatinine, urea, glucose, LDH, sodium, potassium, calcium, phosphate, total protein.
    - Amylasemia, lipasemia, triglyceridemia
    - Proteinuria (strip)
    - Troponine, BNP
    - Serology for Hepatitis B or C, HIV, urine or serum pregnancy tests, sample for chimerism analysis
- Bone marrow aspiration and MRD (flow cytometry)
- All exams needed to document extramedullary relapse: scan, pet-scan, biopsy, ect…

6.2. STUDY SCHEDULE

6.2.1 Pre-inclusion visits (day-30 -7 before the graft)
Information given to the patient by the physician
Verification of pre-inclusion and exclusion criteria
The patient has to sign informed consent before starting conditioning

6.2.2 Inclusion visit (day+30 post-transplant)

Physical examination
Eligibility confirmed based on inclusion/exclusion criteria listed in 4.3 & 4.4
Medical history
Demographic data: sex, date of birth
ECOG performance status assessment
Local laboratory assessment:

- o Standard hematology tests including CBC (hemoglobin, hematocrit, RBC count, WBC count, differential leukocyte count, platelet count), prothrombin time, white cell morphology
- o Blood chemistry: including total bilirubin, AST, ALT, alkaline phosphatase, serum creatinine, urea, glucose, LDH, sodium, potassium, calcium, phosphate, total protein.
- o Amylasemia, lipasemia, triglyceridemia
- o Proteinuria (strip)
- o Troponine, BNP
- o serology for Hepatitis B or C, HIV, urine or serum pregnancy tests, sample for chimerism analysis

Report on associated concomitant medications
Confirmation that the informed consent form has been signed
Confirmation of Complete Remission: bone marrow aspirate/biopsy, MRD, CTscan of thorax, abdomen and pelvis and 18F-FDG PETscan or others
Left ventricular ejection fraction (LVEF), lung function test (DLCO): results from pre-graft evaluation

6.2.3 During ponatinib treatment: every months during 3 months, then every 3 months until 1-year after ponatinib beginning

- Concomitant therapies
- ECOG performance status
- Physical examination, including weight, height, vital signs
- 12- lead ECG
- Chest X-ray

o Laboratory test assessments (§6.2.2) including proteinuria, Troponine, BNP, serology for Hepatitis B

- Bone marrow aspiration: at 12 and 24 months post-transplant or in case of relapse suspicion + MRD
- Other exams to document remission or relapse

LVEF measurement by echocardiography at 6 months, 12 and 24 months from transplant.

6.2.4 At the end of the study (+24 months post-transplant)

In the event of premature study discontinuation, the reason for discontinuation must be documented (withdrawal of consent, SAE, investigator decision, relapse, death, lost to follow-up, therapy failure).

- Concomitant therapies
- ECOG performance status
- Physical examination, including weight, height, vital signs
- 12- lead ECG
- Chest X-ray
- Laboratory test assessments (§6.2.2) including proteinuria, Troponine, BNP
- Bone marrow aspiration + MRD

STUDY SCHEDULE

Activities	D-30 -7 (Pre-inclusion visits)	D+30/+60 (Inclusion visit)	Month 1 ponatinib (day+90)	Month 2 ponatinib (day+120)	Month 3 ponatinib (day+150)	Months +6 /+9/+12 ponatinib (days+240, 330, 420)	End of the study
Patient information	X						
Consent		X					
Inclusion fax / email		X					
Previous medical history		X					
Clinical examination/concomitant therapies/ECOG		X	X	X	X	X	X
12-lead ECG and QTc calculation		x	X	X	X	X	X
LVEF measurement by echocardiography	x					Months 6, 12 and 24	
Chest X-ray	x					Months 6, 12 and 24	X
Analysis (biochemistry, haematology, etc.) including Hep B serology*	X*	X*	X	X	X*	X*	X
Efficacy and/or safety assessment			X	X	X	X	
Compliance			X	X	X	X	X
Adverse events			X	X	X	X	X
Bone marrow aspiration + MRD *in case of relapse suspicion		x	*	*	*	* +months 12 and 24	*+month 24 post-graft

Day 0= day of the graft; MRD: minimal residual disease

6.3. IDENTIFICATION OF ALL DATA SOURCES NOT INCLUDED IN THE MEDICAL RECORD

Not applicable. Data required for follow-up outside the study will be compiled in medical records.

6.4. RULES FOR DISCONTINUING SUBJECT PARTICIPATION

6.4.1. Criteria in respect of early withdrawal of a subject from the study

Treatment with the combination of ponatinib will be stopped prematurely in the event of:

- Non-hematological toxicity CTC grade 3 or 4 attributed to ponatinib (DLT).
- Lack of recovery of hematological or non-hematological toxicity CTC grade 3 or 4, or toxicity still present 45 days after the start of ponatinib.
- Study therapy must be immediately discontinued in the event of serious cardiovascular effect.
- Reasons other than toxicity:
  - Patients have the right to withdraw form the study at any time and for any reason.
  - The investigator has the right to withdraw patients from the study in case of intercurrent illness, adverse event and treatment failure after a prescribed procedure, protocol violations, administrative or other reasons. An excessive rate of withdrawals can render the study uninterpretable; therefore unnecessary withdrawals should be avoided.
  - There is evidence of relapse.
  - Discontinuation of therapy would be in the best interest of the patient.
  - A patient is unable to comply with the protocol

A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study. If the reason for removal from the study is an adverse event or an abnormal laboratory test result, the principal specific event or test will be recorded on the CRF.
Patients withdrawn prematurely will be followed for progression and survival after the end of the study treatment.

6.4.2. Procedures in respect of early withdrawal of a subject from the study

The study will be discontinued early, if:

- There is evidence of unacceptable treatment related mortality (see statistical section).
- The incidence or severity of adverse events in this study or other studies with ponatinib indicates a potential health hazard to patients.

6.4.3. Criteria in respect of discontinuation of all or part of the study (excluding biostatistical considerations)

A definitive or temporary discontinuation of all or part of the study may be decided by ANSM, the ERB, Sponsor or Data and Safety Monitoring Committee (DSMC).
In case of early discontinuation of the study decided by the Sponsor or DSMC, ANSM and the ERB shall be informed within less than 15 days by mail.

In any case:
- A written confirmation of this early discontinuation of the study shall be sent to the coordinating investigator of the study (specifying the reasons for the early discontinuation) and to the principal investigator of each centre (if applicable),
- All the patients included in the study shall be informed and should attend their early withdrawal visit.

The study will be discontinued early, if:

- There is evidence of unacceptable treatment related mortality.
- The incidence or severity of adverse events in this study or other studies with ponatinib indicates a potential health hazard to patients.

Severe adverse events of interest in the context of ponatinib are mainly cardiovascular events and less frequently pancreatic toxicity. In the case of occurrence of any Grade 3-4 event of interest related to ponatinib, recruitment will be temporally stopped and a safety report will be transmitted to the DSMB.

If the proportion of patients experiencing a Grade 3-4 event of interest related to ponatinib exceeds 20% after the inclusion of the 10 first patients, DSMB will decide wether the study has to be discontinued. If the proportion of patients experiencing Grade 3-4 event of interest related to ponatinib is less than 20%, then the recruitment will continue for 10 more patients and safety will be reevaluated following the same procedure.

6.5. PATIENT MEDICAL CARE AT THE END OF THE STUDY

After the study is closed or after the two-year follow-up (from day+0), medical care for patients is at the discretion of the investigators.

6.6. FINAL STUDY REPORT

The final study report includes the full written description of the study.

This report should be sent to the competent authorities and the ethical review board less than one year after the end of the study.

7. DATA MANAGEMENT AND STATISTICS

7.1. STUDY DATA COLLECTION AND PROCESSING

7.1.1. Data collection

A Case Report Form (eCRF) shall be drawn up for each subject. All information required by the protocol should be provided in the eCRF. It should include data required to confirm compliance with the protocol and all data necessary for statistical analysis, and identify major deviations from the protocol.

The person(s) responsible for completing the CRF/eCRF (investigator, CRA) should be defined and identified in the responsibility delegation table for each centre (kept in the investigator's file).

7.1.2. Data encoding

By signing this protocol, the principal investigator and all the co-investigators undertake to keep the identities of the patients taking part in the study confidential.

This code should be the only information featuring in the eCRF enabling a retrospective link with the patient.
The investigator shall also encode the patient data on any documents that may be in its possession (imaging, biology test reports, etc.) attached to the eCRF.

CNIL recommends limiting patient identification to initials (=the first letter of the first name and last name, supplemented by a number assigned at the time of patient inclusion).We will use this coding rule.

7.1.3. Data processing

Clinical data collection shall be based on a database and creating input templates similar to the CRF in compliance with the protocol and applicable regulations.
The structure of the database and data input screens shall be approved by the trial sponsor.
At the end of the study, database reconciliation is carried out between the CRF database and safety database. This reconciliation is performed before database locking. Similarly, an annual reconciliation is carried out when updating the Annual Safety Report (ASR).

7.2. STATISTICS

77 patients will be included in the study.

Name and contact details of analysis manager:
Dr Myriam Labopin, Hopital St-Antoine, PARIS, France.

7.2.1. Description of planned statistical methods, including planned intermediate analysis schedule

This is a single-Stage Phase II Clinical Trial. The analysis will be done according to the intent-to-treat principle, with no intermediate analysis.

Analysis of subgroups: the following sub-groups will be considered: according to age (< or >median), gender, disease characteristics (cytogenetics, molecular status) and status of disease before transplant, type of conditioning regimen (myeloabaltive vs reduced-intensity).

7.2.2. Statistical justification of the number of inclusions

We used a one step A'Hern procedure. Let's P0 the maximum response proportion of a poor drug equal to 70%, and P1 the minimum response proportion of a good drug equal to 85%. P is the proportion of responding, ie without relapse. This study is designed for testing H0: $P \leq P0$ versus H1: $P \geq P1$. The study requires 69 subjects to decide whether the proportion responding, P, is less than or equal to 70% or greater than or equal to 85%.
We should anticipate a drop-out, ie a percentage of patients for whom no response data will be collected (NRM, lost to Follow-up), of 10% (8 non evaluable patients). As such the number of patients who will be included is 77.

7.2.3. Expected level of statistical significance

In this single-Stage Phase II Clinical Trial using a one step A'Hern procedure, alpha is the probability of rejecting that $P \leq 70\%$ when this is true. Beta is the probability of rejecting that $P \geq 85\%$ when this is true. If the number of responses is 55 or more, the hypothesis that $P \leq 70\%$ is rejected with a target error rate alpha of 5% and an actual error rate of 4.8%. If the number of responses is 54 or less, the hypothesis that $P \geq 85\%$ is rejected with a target error rate beta of 10% and an actual error rate of 8.5%.

7.2.4. Statistical criteria for discontinuation of study

No intermediate analysis is planned in this study. All patients receiving at least one day of ponatinib will be included in the statistical analysis.

7.2.5. Consideration method for missing, unused or invalid data

Patients with hematological or extramedullary relapse before starting ponatinib will be excluded from the study. Follow-up of these patients will be at the discretion of the investigator. Also, these patients have to be replaced one by one.

7.2.6. Management of changes made to the initial analytical strategy

Not applicable

7.2.7. Choice of subjects to be included in analysis

All patients receiving at least one day of ponatinib will be included in the statistical analysis.

7.2.8. Randomisation

Not applicable

8. PHARMACOVIGILANCE AND ADVERSE EVENT MANAGEMENT

8.1. DEFINITIONS

Abuse	This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
Adverse events (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of medicinal product, whether or not considered related to the medicinal product.
Adverse Event Intensity (EvI)	Any event in the selected classification should be rated as follows: 1 = mild 2 = moderate 3 = severe 4 = life-threatening 5= death
Adverse reactions (AR)	All untoward and unintended responses to an investigational medicinal product related to any dose administered. The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product. It implies a reasonable possibility of a causal relationship between the event and the investigational medicinal product (IMP). Any untoward and unintended response to a non-IMP which does not result from a possible interaction with an IMP is, by definition, not a SUSAR.
Medication Error	Medication errors are unintended mistakes in in the prescribing, dispensing and administration of a medicine that could cause harm to a patient. They are the most common preventable cause of undesired adverse events.
Misuse	This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information.
Overdose	This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information. Clinical judgement should always be applied.
Serious adverse events (SAE)	Any untoward medical occurrence or effect that at any dose results in death is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or

	significant disability or incapacity, or is a congenital anomaly or birth defect. Some medical events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered as “serious” in accordance with the definition. Serious adverse events occurring to a subject after the treatment of that subject has ended should be reported to the sponsor if the investigator becomes aware of them.
Unexpected adverse reactions (UAR)	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product).
Vigilance	Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.

8.2. SAFETY EVALUATION PARAMETERS

There will be no additional parameters other than the efficacy evaluation parameters described above.

8.3. LIST OF EXPECTED ARS

Within the scope of this protocol, the expected ARs are associated with:

Ponatinib: haematological toxicity, pancreatitis, QTc prolongation, cardio-vascular events **(ANNEXE 4 & see investigator brochure)**

The disease: aplasia, infections, haemorrhage, metabolic disorders, compressive tumour, relapse and deaths.

The transplant: hospitalization in sterile unit 4 to 6 weeks, risks related to clinical and biological exams, infections, acute and chronic GVHD, immunosuppressive drugs toxicities, catheter need with risks of pains, infections.

Some non-serious ARs may be reported to the sponsor, at the discretion of the investigator.

8.4. ADVERSE EVENT MANAGEMENT

8.4.1. SAR/SAE reporting

All SARs/SAEs *w*hether expected or unexpected, require the completion of a SAR/SAE report. The investigator should check that the information entered in this form is accurate and clear (no abbreviations, etc.). The SAR report and the documents attached to this report shall be encoded.
SARs/SAEs should be reported immediately (within 24 hours of the investigator becoming aware of the event) to the sponsor.
On receipt of a USAR report, the sponsor reports it to the supervisory authorities. Once a year, an annual safety report is drafted.
NB: Pregnancy, overdose, misuse, medication errors or potential medication errors, quality defects should be notified by the investigator to the sponsor even if there is no adverse reaction.

Sponsor contact: **Mrs Laure Morisset,**
DRCI, CH de Versailles, 177 rue de Versailles, 78157 Le Chesnay Cedex; Tel: +33 (0)139239785; Fax: +33 (0)139239773;
e-mail: lmorisset@ch-versailles.fr

8.4.2. Data and Safety Monitoring Committee (DSMC)

The DSMC is an advisory committee responsible for reviewing the safety of a clinical trial for the sponsor and the coordinator of the study. Its members, well-versed in the field of clinical trials (pathology and methodology), are not involved in the study. They are appointed for the duration of the study and undertake to take part and observe data confidentiality. The members of the DSMC are selected collectively by the coordinator and the sponsor. The DSMC receives the annual safety reports and may be consulted by the monitor if a SUSAR or SAR involves a specific analytical problem or in the event of doubt on the risk benefit arising in the course of the study.
The list of members of the DSMC is attached in **ANNEXE 3**.

8.5. FOLLOW-UP PROCEDURE AND PERIOD FOR SUBJECTS FOLLOWING THE ONSET OF ADVERSE EVENTS

All events must be followed until the cure, healing or death. In case of premature treatment discontinuation, the patient should continue to come to all relevant follow-up visits. If a patient fails to keep the appointments for study visits, the investigator will document the reason and circumstances as completely and accurately as possible..
NB: pregnancy occurring during the study should be followed at least until the birth.
NB: an AE delayed (malformation, secondary cancer…) must be declared to Sponsor (if Investigator is informed about this event) even after the end of the study.

9. ADMINISTRATIVE AND REGULATORY ASPECTS

9.1. SOURCE DATA AND DOCUMENT ACCESS RIGHTS

Each patient's medical data shall only be provided to the sponsor or any person duly authorised by the sponsor, and, where applicable, to authorised health authorities, in confidential conditions.
The sponsor and the supervisory authorities may request direct access to medical records for the purposes of verification of the procedures and/or data in respect of the clinical trial, within the limits authorised by the legislation and regulations.
The data compiled during the trial may be processed electronically in compliance with CNIL requirements (compliance with French Reference Methodology MR001).

9.2. TRIAL MONITORING

Monitoring visits (investigators center and pharmacy center) will be scheduled regularly by a Clinical Research Assistant (CRA) representing the sponsor.
During these visits, the CRA will review study plan compliance, adherence to the protocol, and data quality. The CRA will compare CRFs and ensure that the study is being conducted in compliance with pertinent regulatory requirements.

The protocol has been classified according to the estimated level of subject risk:
Risk C: High predictable risk

The investigator will provide the CRA with direct access to CRFs and to the subject's records (e.g., medical records, office charts, hospital charts, and study-related charts) for source data verification, as well as to any other study documents.

9.3. INSPECTION / AUDIT

As part of this study, an inspection or audit may take place. Sponsor and study centers must give an access to the data to inspectors or auditors.

9.4. ETHICAL CONSIDERATIONS

9.4.1. Written informed consent

The investigator agrees to provide the subject with clear and precise information about the protocol and request him/her for written informed consent (information form and consent form

appended). The investigator will give the subject a copy of the information form and consent form. The subject can only be enrolled in the study after reading the information form and signing and dating the consent form. If this is not possible, a third party (independent from the study) proves the subject's consent. The investigator should also sign and date the consent form. Both documents should be issued at least in duplicate hard copy format so that the patient and the investigator can each keep a copy. The investigator's original will be placed in the investigator's file.

9.4.2. Emergency consent form collection

Not applicable

9.4.3. Ethical Review Board

The sponsor agrees to submit the study to an Ethical Review Board for prior approval. The information disclosed relates to the procedure and nature of the study and the guarantees provided for subjects participating in the study.

9.5. AMENDMENTS TO THE PROTOCOL

Requests for substantial modifications should be addressed by the sponsor for approval or notification to ANSM and/or the Ethical Review Board concerned in compliance with the law 2004-806 of August 9, 2004 and its implementing decrees.

The amended protocol should be a dated updated version. If necessary, the information form and consent form should be amended.

9.6. REGISTRATION WITH THE COMPETENT AUTHORITIES

For this protocol, a request will be addressed to the ANSM for approval.

9.7. NATIONAL REGISTER OF SUBJECTS UNDERGOING BIOMEDICAL RESEARCH

Not applicable

9.8. STUDY FUNDING AND INSURANCE

The sponsor shall fund the study and take out an insurance policy covering the financial consequences of its civil liability in compliance with the regulations.

9.9. PUBLICATION RULES

A copy of the publication will be delivered to the CH of Versailles, the study sponsor, which will necessarily be mentioned. The authors will be determined in proportion to the number of subjects enrolled. The coordinator shall draw up the list of authors.

9.10. OUTCOME OF BIOLOGICAL SAMPLES

Not applicable

9.11. SOURCE DATA ARCHIVING

Investigator should archive all study data for at least 15 years after the end of the study.
At the end of the study, Investigator will receive by Sponsor, a CD-ROM included a copy of patient(s) data in his center. On specific request, this CD-ROM may contains input comments, queries history and audit trail report.

LIST OF APPENDICES

APPENDIX 1: INVESTIGATOR LIST

Center number	SURNAME, FIRST NAME	Area of medicine	Title	Name of institution	Name and address of affiliated department	Telephone, fax and e-mail
1	Pr Chevallier	Hematology	MD PhD	CHU Nantes	Hematology	0240083994 patrice.chevallier@chu-nantes.fr
2	Pr Mohamad Mohty	Hematology	MD PhD	Hopital st-Antoine	Hematology	Mohamad.mohty@inserm.fr
3	Pr Regis Peffault de La Tour	Hematology	MD PhD	Hopital St-Louis	Hematology	regis.peffaultdelatour@aphp.fr
4	Dr Anne Huynh	Hematology	MD	CRLC Toulouse	Hematology	huynh.anne@iuct-oncopole.fr
5	Dr Pascal Turlure	Hematology	MD	CHU Limoges	Hematology	pascal.turlure@chu-limoges.fr
6	Dr Natacha Maillard	Hematology	MD	CHU Poitiers	Hematology	natacha.maillard@chu-poitiers.fr
7	Pr Marie-Theres Rubio	Hematology	MD PhD	CHU Nancy	Hematology	mt_rubio@hotmail.com
8	Pr Ibrahim Yakoub-Agha	Hematology	MD PhD	CHU Lille	Hematology	Ibrahim.YAKOUBAGHA@CHRU-LILLE.FR
9	Dr Sylvain Chantepie	Hematology	MD	CHU Caen	Hematology	Chantepie-s@chu-caen.fr
10	Dr Romain GUIEZE	Hematology	MD	CHU Clermont-Ferrand	Hematology	rguieze@chu-clermontferrand.fr
11	Dr Gaelle Guillerm	Hematology	MD	CHU Brest	Hematology	gaelle.guillerm@chu-brest.fr
12	Dr Sylvie Francois	Hematology	MD	CHU Angers	Hematology	SYFrancois@chu-angers.fr
13	Dr Helene Labussiere	Hematology	MD	CHU Lyon	Hematology	helene.labussierehu-lyon.fr
14	Dr Claude-Eric Bulabois	Hematology	MD	CHU Grenoble	Hematology	CEBulabois@chu-grenoble.fr

APPENDIX 2: SUMMARY OF PROTOCOL

	Phase 2 study of Ponatinib (Iclusig) for prevention of relapse after allogeneic stem cell transplantation (allo-SCT) in FLT3-ITD AML patients: the A-PO-LLO trial.
Sponsor	**CH de Versailles**
Principal investigators	**Patrice Chevallier**, Hematology, University Hospital, Nantes
Type of study	This will be an open-label, multicentre phase 2 study investigating the efficacy of ponatinib for relapse prevention in allografted FLT3-ITD AML patients in response at transplant
Number of patients	77
Rational	Recent advances in acute myeloid leukemia (AML) have been characterized by a better understanding of disease biology. As such, FMS-like tyrosine kinase 3-internal tandem duplication (FLT3-ITD) have been recognized as conferring a poor prognosis. The FLT3-ITD molecular mutation is observed in about one-quarter of patients diagnosed with AML. Patients presenting with this abnormality are referred for early allogeneic stem-cell transplantation (allo-SCT). However, some data suggest that FLT3-ITD remains associated with a poor prognosis even after allo-SCT because of higher risk of relapse and strategies for preventing relapse in the post-transplant setting are required (Hu et al, Expert Rev Hematol, 2014). For example, in a large cohort of patients (Brunet et al, JCO, 2012), the incidence of relapse for FLT3-ITD AML patients after allo-SCT was 30% at 2-years, significantly higher compared to FLT3-ITD negative patients (p=0.006). Ponatinib (Iclusig®) is an orally available, tyrosine kinase inhibitor with a unique binding mechanism allowing inhibition of BCR-ABL kinases, including those with the T315I point mutation. Ponatinib also has in vitro inhibitory activity against a discrete set of kinases implicated in the pathogenesis of other hematologic malignancies, including FLT3, KIT, fibroblast growth factor receptor 1 (FGFR1), and platelet derived growth factor receptor α (PDGFRα). In vitro activity of ponatinib in AML has been already demonstrated (Gozgit et al, *Mol Cancer Ther,* 2011; Smith et al, *Blood* 2013). If some trials are on-going to test ponatinib alone or in combination with chemotherapy in FLT3-ITD AML (Clinical.trials.gov), no study is dedicated to the use of ponatinib in the post-transplant setting in order to prevent relapse in these patients. The main goal of this study will be to determine the maximal tolerated dose (MDT) of ponatinib after allo-SCT in FLT3-ITD AML patients, then to investigate the efficacy of ponatinib in a larger cohort of patients
Primary endpoints	• Relapse incidence at 2 years from transplant
Secondary endpoints	• Overall survival (OS) at 2 year • Leukemia-free survival (LFS) at 2 year • Non-relapse mortality (NRM) at day+100, 1-year and 2-year • Acute and chronic GVHD • T, B and NK cell reconstitutions at +3, +6, +9 and +12 months post-transplant • Chimerism at day 30, 60, 90, +6, +12 months post-transplant • Rate of patients who will stop ponatinib during the first year of transplant and reasons for stopping ponatinib (relapse, toxicity, other…) • To evaluate safety particularly for VOEs. • To evaluate minimal residual disease (MRD): before graft and at each myelogram performed after allograft
Inclusion criteria	- Having or not received previously ponatinib - Patient affiliated to or beneficiary of the French National Health Service - Age ≥ 18 and ≤ 70 - Positive FLT-3 ITD AML in complete remission at time of ponatinib beginning - Patient eligible for an allo-SCT (myeloablative, sequential or reduced-intensity) o Any type of donor without contra-indication for stem cell mobilization - Have an Eastern Cooperative Oncology Group (ECOG) performance status < 2 - Have adequate renal function: Serum creatinine ≤ 1.5 × upper limit of normal (ULN) for institution - Have adequate hepatic function: Total serum bilirubin ≤ 1.5 × ULN, unless due to Gilbert's syndrome; Alanine aminotransferase (ALT) ≤ 2.5 × ULN, or ≤ 5 × ULN if leukemic infiltration of the liver is present ; Aspartate aminotransferase (AST) ≤ 2.5 × ULN, or ≤ 5 × ULN ifleukemic infiltration of the liver is present - Have normal pancreatic status: Serum lipase and amylase ≤ 1.5 × ULN - Have normal QTcF interval on screening electrocardiogram (ECG) evaluation,defined as QTcF of ≤ 450 ms in males or ≤ 470 ms in females. - Platelets ≥ 100 Giga/l; Neutrophils ≥ 1 Giga/l - Have a negative pregnancy test documented prior to enrollment (for females of childbearing potential). - Agree to use an effective form of contraception with sexual partners throughout study participation (for female and male patients who are fertile). - Provide written informed consent.

	- Be willing and able to comply with scheduled visits and study procedures.
• Exclusion criteria	• HIV positive, active Hepatitis B or C • Childbearing or childbreast feading women • Women or men without effective contraceptive barrier if needed • Previous myocardial infarction, or cerebral vascular accident, pancreatitis • Creatinine clearance ≤ 50 ml/min • Contra-indication to ponatinib • Previous or concurrent second malignancy except for adequately treated basal cell carcinoma of the skin, curatively treated in situ carcinoma of the cervix, curatively treated solid cancer, with no evidence of disease for at least 2 years • Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule • Patients at high or very high risk of cardiovascular disease with any of the following • a) Established cardiovascular disease Cardiac disease: • - Congestive heart failure greater than class II NYHA or • - Left ventricular ejection fraction (LVEF) < 50% or • - Unstable angina (anginal symptoms at rest) or • - New onset angina (began within the last 3 months) or • - Myocardial infarction, coronary/peripheral artery disease, congestive heart failure, cerebrovascular accident including transient ischemic attack within the past 12 months or • - History of thrombolic or embolic events Arrhythmias • - Any history of clinically significant cardiac arrhythmias requiring anti-arrhythmic therapy. • b) Diabetes Mellitus, • c) Arterial Hypertension, - Uncontrolled hypertension defined as systolic blood pressure greater than 140 mmHg or diastolic pressure greater than 90 mmHg, despite optimal medical management and optimal measurement • (http://www.has-sante.fr/portail/display.jsp?id=c_272459) - Any history of hypertension with • - Hypertensive encephalopathy • - Posterior leucoencephalopathy • - Aortic or artery dissection • d) Familial dysplipidemia. • e) Taking medications that are known to be associated with Torsades de Pointes (see Appendix 11)
Pretreatment work-up	o Clinical history and physical examination. This should include: previous medical history and treatment. Physical examination, ECOG performance status; height, weight and body surface area (BSA). o Complete blood cell count, bilirubin (direct and total), alkaline phosphatase, gammaGT, ALAT, ASAT, LDH, CRP, Na, K, Ca, uric acid, glucose, serum BUN, serum creatinine, total proteins ; serum albumin and protein electrophoresis, amylase, lipase, cholesterol, triglyceride uric acid o HIV, Hepatitis B and C tests. o betaHCG o Left ventricular ejection fraction by radionuclide ventriculography or echocardiography, electrocardiogram o DLCO o Bone marrow aspiration for documentation of CR before transplant o All exams which were initially abnormal and which are necessary for documentation of response before transplant
Treatment scheme	Ponatinib administration will start for all patients at day+60 (if engraftment confirmed) 77 patients will receive ponatinib at a dose of 30 mg/day for 1-year. The dose of ponatinib will be adjusted according to toxicity with possibility to reduce the dose at 15 mg/day when toxicities due to this drug will be resolved. After 1 year of ponatinib treatment, physicians will be allowed to stop or pursue TKI (ponatinib or other one) at their discretion and own expenses.
Follow-up	• Physical examination every week up to day+100 then every month up to 2 years from day 0. • Complete blood counts, renal and hepatic work-up, amylase, lipase, each week until day+100 then each month until 2 years post-transplant. • Left ventricular ejection fraction and electrocardiogram at 6 months and 1 and 2 years post-transplant. . • All exams which were initially abnormal and which are necessary for response evaluation or needed in case of relapse suspicion. • T, B and NK cell reconstitutions at +3, +6, +9 and +12 months post-transplant • Chimerism at day 30, 90, +6, and +12 months post-transplant • MRD before graft and during treatment
Efficacy assessment	• Leukemia free survival**:** time interval from the date of the graft until the date of last follow-up, death or relapse • Overall survival:: time interval from the graft until the date of last follow-up or death • Toxicity: (NCI CTC version 4) • GVHD: NIH score
Statistical consideration	• We used a one step A'Hern procedure. Let's P0 the maximum response proportion of a poor drug equal to 70%, and P1 the minimum response proportion of a good drug equal to 85%. P is the proportion of responding, ie without relapse. This study is designed for testing H0: P ≤ P0 versus H1: P ≥ P1. The study requires 69 subjects to decide whether the proportion responding, P, is less than or equal to 70% or greater than or equal to 85%. • We should anticipate a drop-out, ie a percentage of patients for whom no response data will be collected (NRM, lost to Follow-up), of 10% (8 non evaluable patients). As such the

	number of patients who will be included is 77. • Dr Myriam Labopin (Hopital st-Antoine, Paris) will be the statistician for the study.
Time schedule	• Planned start of the trial: Mai 2018 • Duration of accrual: 24 months • Follow-up: 2 years. • End of the study: December 2021
Financial support	• INCYTE

APPENDIX 3: DATA AND SAFETY MONITORING COMMITTEE

Members of the safety monitoring committee:

Name	Hospital
Pr Arnaud PIGNEUX	Service d'Hématologie Clinique et Thérapie Cellulaire CHU Bordeaux
Dr Nathalie DHEDIN	Service AJA/Hematologie, APHP, Hôpital St-Louis, Paris
Dr Ana BERCENEANU	Service d'Hematologie, CHU Besancon

APPENDIX 4: DOSE MODIFICATIONS OF PONATINIB FOR TOXICITY

Hematological toxicity (except anemia)

ANC < 1 x 10^9/l and/or platelets < 50 x 10^9/l during maintenance	1. Stop ponatinib until ANC ≥ 1 x 10^9/l and platelets ≥ 100 x 10^9/l. 2. Resume ponatinib at the same dose level after recovery.
Subsequent occurence	1. Stop ponatinib until ANC ≥ 1 x 10^9/l and platelets ≥ 100 x 10^9/l. 2. Resume ponatinib at a lower dose level after recovery. 3. Patient already at 15 mg, Stop ponatinib

The treatment of anemic patients with Rhu-EPO is allowed.

Non-hematological toxicity

Grade 2 non-hematological toxicity related to ponatinib	1. Stop ponatinib. 2. Resume ponatinib at previous dose (i.e. before adverse reaction) if toxicity decreases to grade ≤ 1.
Grade 3-4 non-hematological toxicity related to ponatinib despite supportive care	1. Stop ponatinib 2. Resume ponatinib at previous dose (i.e. before adverse reaction) if toxicity decreases to grade ≤ 1. 3. Second episode despite dose reduction : Stop ponatinib and do not resume ponatinib.

Pancreatitis

Ponatinib therapy could induce pancreatic enzymes elevation. In this case, it is recommended to perform a CT scan. In case of pancreatitis grade 2, Ponatinib should be interrupted until the toxicity decrease to ≤ grade 1. In case of pancreatitis grade 3 or 4, Ponatinib will not be resumed.

Grade 2 pancreatitis	1. Stop ponatinib. 2. CT scan of the pancreas 3. In case of radiological pancreatitis stop until complete normalization 4. In the absence of radiological pancreatitis, resume at same dose if grade ≤ 1 5. In case of recurrence, resume at a lower dose level
Grade 3 pancreatitis	1. Stop ponatinib. 2. CT scan of the pancreas 3. In case of radiological pancreatitis stop until complete normalization 4. In the absence of radiological pancreatitis, resume at a lower dose level 5. In case of recurrence, do not resume ponatinib
Grade 4 pancreatitis	1. Stop ponatinib. 2. Do not resume ponatinib.

QTc prolongation

Ponatinib therapy could induce QTc prolongation. In case of QTc grade 4, Ponatinib will not be resumed.

QTc can be calculated according to the Bazett formula: QTcb (ms) = QT (ms) / RR0.5 (sec)

Grade 2 (QTc 481-500 ms)	1. Stop ponatinib. 2. Perform serum electrolyte analysis (including potassium, calcium and magnesium) and correct with supplements if below normal limits. Review concomitant medications. Repeat ECG as clinically indicated, but at least daily until QTc returns to ≤ grade 1 (480 ms) 3. Resume ponatinib after recovery to ≤ grade 1 4. If no contributing reason was identified for QTc elevation then weekly ECG monitoring is recommended for 4 weeks upon resumption of ponatinib, then monthly for 6 months, and then every 3 months for the remainder of the study, or more frequently as clinically indicated 5. In case of recurrence, repeat above 6. In the absence of recove
Grade 3 (QTcF ≥ 501 ms on at least 2 separate ECGs)	1. Stop ponatinib. 2. Monitor the patient at hospital with a cardiologist. until QTc returns to ≤ grade 1 (480 ms) 3. Resume ponatinib after recovery to ≤ grade 1 4. If no contributing reason was identified for QTc elevation then weekly ECG monitoring is recommended for 4 weeks upon resumption of ponatinib, then monthly for 6 months, and then every 3 months for the remainder of the study, or more frequently as clinically indicated 5. In case of recurrence, repeat above 6. In the absence of recovery to ≤ grade 1, the patient has to stay at hospital, consider DLT and contact a cardiologist and DSMB.
Grade 4	1. Stop ponatinib. 2. Do not resume ponatinib and consider DLT. 3. Monitor the patient at hospital with a cardiologist.

APPENDIX 5: ECOG PERFORMANCE STATUS

Grade Performance Status

0 Able to carry out all normal activity without restriction

1 Restricted in physicaly strenuous activity but ambulatory and able to carry out light work

2 Ambulatory and capable of all selfcare but unable to carry out any work; up about more than 50%of walking hours.

3 Capable of limited selfcare
Confined to bed or chair more than 50% of waking hours

4 Completely disabled; cannot carry any selfcare
Totally confined to bed or chair

APPENDIX 6: DRUGS WITH RISK OF TORSADE DE POINTES

http://www.azcert.org/medical-pros/drug-lists/list-01.cfm?sort=Generic_name

Generic Name	Brand Name	Class/Clinical use	Comments
Amiodarone	Cordarone®	Anti-arrhythmic / abnormal heart rhythm	Females>Males,TdP risk regarded as low
Amiodarone	Pacerone®	Anti-arrhythmic / abnormal heart rhythm	Females>Males,TdP risk regarded as low
Arsenic trioxide	Trisenox®	Anti-cancer / Leukemia	
Astemizole	Hismanal®	Antihistamine / Allergic rhinitis	No Longer available in U.S.
Azithromycin	Zithromax®	Antibiotic / bacterial infection	
Bepridil	Vascor®	Anti-anginal / heart pain	Females>Males
Chloroquine	Aralen®	Anti-malarial / malaria infection	
Chlorpromazine	Thorazine®	Anti-psychotic/ Antiemetic / schizophrenia/ nausea	
Cisapride	Propulsid®	GI stimulant / heartburn	No longer available in U.S.
Citalopram	Celexa®	Anti-depressant / depress	
Clarithromycin	Biaxin®	Antibiotic / bacterial infection	
Disopyramide	Norpace®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Dofetilide	Tikosyn®	Anti-arrhythmic / abnormal heart rhythm	Females > Males
Domperidone	Motilium®	Anti-nausea / nausea	Not available in U.S.
Droperidol	Inapsine®	Sedative;Anti-nausea / anesthesia adjunct, nausea	
Erythromycin	E.E.S.®	Antibiotic; GI stimulant / bacterial infection; increase GI motility	Females>Males
Erythromycin	Erythrocin®	Antibiotic; GI stimulant / bacterial infection; increase GI motility	Females>Males
Flecainide	Tambocor®	Anti-arrhythmic / abnormal heart rhythm	
Halofantrine	Halfan®	Anti-malarial / malaria infection	Females>Males
Haloperidol	Haldol®	Anti-psychotic / schizophrenia, agitation	TdP risk with I.V. or excess dosage
Ibutilide	Corvert®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Levomethadyl	Orlaam®	Opiate agonist / pain control, narcotic dependence	Not available in U.S.
Mesoridazine	Serentil®	Anti-psychotic / schizophrenia	
Methadone	Dolophine®	Opiate agonist / pain control, narcotic dependence	Females>Males

Methadone	Methadose®	Opiate agonist / pain control, narcotic dependence	Females>Males
Moxifloxacin	Avelox®	Antibiotic / bacterial infection	
Pentamidine	NebuPent®	Anti-infective / pneumocystis pneumonia	Females>Males
Pentamidine	Pentam®	Anti-infective / pneumocystis pneumonia	Females>Males
Pimozide	Orap®	Anti-psychotic / Tourette's tics	Females>Males
Probucol	Lorelco®	Antilipemic / Hypercholesterolemia	No longer available in U.S.
Procainamide	Pronestyl®	Anti-arrhythmic / abnormal heart rhythm	
Procainamide	Procan®	Anti-arrhythmic / abnormal heart rhythm	
Quinidine	Quinaglute®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Quinidine	Cardioquin®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Sevoflurane	Ulane®	Anesthetic, general / anesthesia	Label warning for patients with congenital long QT or patients taking QT prolonging drugs
Sevoflurane	Sojourn®	Anesthetic, general / anesthesia	Label warning for patients with congenital long QT or patients taking QT prolonging drugs
Sotalol	Betapace®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Sparfloxacin	Zagam®	Antibiotic / bacterial infection	No longer available in U.S.
Terfenadine	Seldane®	Antihistamine / Allergic rhinitis	No longer available in U.S.
Thioridazine	Mellaril®	Anti-psychotic / schizophrenia	
Vandetanib	Caprelsa®	Anti-cancer / Thyroid cancer	

Source: www.QTdrugs.org
Drugs on the QT Drug Lists are reviewed on an ongoin g basis to assure that the availa ble evidence supports their continued placement on their respective list.

KEY

Females > Males:
Substantial evidence indicates that there is a greater risk of TdP in women (usually > twofold).

CredibleMeds, AZCERT, Inc.
Oro Valley, Arizona

Disclaimer and Waiver

The information presented is intended solely for the p urpose of providing general infor mation about health related matters. It is not intended for any other purpose, including, but not limited to, medical or pharmaceutical advice and/or treatment, nor is it intended to substitute for the users' relationships with their own health care/pharmaceutical providers. To that extent, by continued use of this website and the information it contains, the user affirms the understanding of the purpose and releases AZCERT, Inc., The University of Arizona, State of Arizona and Arizona Board of Regents from any claims arising out of his/her use of the website.

APPENDIX 7 : NOTE D'INFORMATION PATIENT

	LETTRE D'INFORMATION POUR PARTICIPATION A UNE RECHERCHE INTERVENTIONNELLE
Version	Version n° 1.2- 19/03/2018
Eudract	***2017-004282-28***
Protocole	"Phase 2 study of Ponatinib (Iclusig) for prevention of relapse after allogeneic stem cell transplantation (allo-SCT) in FLT3-ITD AML patients: the PONALLO trial." « Etude de Phase 2 testant le Ponatinib (Iclusig) en prévention de la rechute post-allogreffe pour des patients atteints de leucémie aigue myéloblastique FLT3-ITD positive : Etude PONALLO."

LES CONTACTS IMPORTANTS :

Le promoteur de la recherche :

CH de Versailles

Direction de la recherche

✉ lmorisset@ch-versailles.fr

☎ 01.39.23.97.85

Le médecin-investigateur coordonnateur de la recherche :

Pr Chevallier Patrice /CHU de Nantes

✉ Service d'hématologie clinique

Place Alexis Ricordeau

☎ Tel : **02 40 08 39 94**

Patrice.chevallier@chu-nantes.fr

Madame, Monsieur,

Vous êtes actuellement traité(e) pour une leucémie aigue myéloblastique (LAM) et il est nécessaire de réaliser une allogreffe de cellules souches hématopoïétiques (allo-CSH) pour votre maladie. Dans ce cadre, nous vous proposons de participer à une recherche biomédicale intitulée « Etude de Phase 2 testant le Ponatinib (Iclusig) en prévention de la rechute post-allogreffe pour des patients atteints de leucémie aigue myéloblastique FLT3-ITD positive : Etude PONALLO."

Après la chimiothérapie, l'allogreffe représente le meilleur traitement de consolidation afin d'éviter une récidive de votre maladie. Malheureusement un certain nombre de rechutes post-greffe surviennent encore aujourd'hui, raison pour laquelle des stratégies de prévention de cette rechute sont développées afin d'éviter au maximum ce risque.

Il se trouve que les cellules leucémiques de votre maladie expriment une mutation de gène particulière appelée FLT3-ITD qui peut aujourd'hui être accessible à un traitement que l'on appelle ciblé.

Cette recherche qui vous est proposée a pour but d'administrer comme traitement de prévention de la rechute post-greffe, du ponatinib ou Iclusig®, un médicament anti-FLT3-ITD, administré à la fin du deuxième mois post-greffe par la bouche en une prise par jour et pour une durée de un an.

Le CH de Versailles est le promoteur de cette recherche, c'est à dire qu'il en est responsable et qu'il l'organise.

Votre participation à la recherche, dans le cas où vous donneriez votre accord, ne pourra vous être confirmée qu'à la condition que vous remplissiez tous les critères d'inclusion pour participer à cette recherche.

COMMENT VOUS DECIDER ?

- Votre médecin-investigateur vous a expliqué le protocole. Ce protocole est résumé dans ce document intitulé « note d'information ». Nous vous recommandons de lire attentivement cette note d'information avant de vous décider. Vous pouvez si vous le souhaitez en discuter avec votre médecin traitant ou avec vos proches. N'hésitez pas à joindre votre médecin hématologue si vous désirez avoir des précisions sur certains points. Vous avez un délai de réflexion de 10 jours avant de vous décider.

- Votre acceptation ou votre refus ne modifiera en rien les rapports que vous aurez avec votre médecin hématologue qui continuera de vous proposer les soins qui lui paraissent les plus adaptés à votre état de santé. Si vous acceptez de participer à cette recherche, nous vous demanderons de signer une attestation de consentement. Cette attestation sera aussi signée par votre médecin-investigateur. Cette signature confirmera que vous êtes d'accord pour participer à la recherche. Votre signature est indispensable, ainsi que celle du médecin-investigateur. Même après avoir signé pour donner votre accord de participation, vous garderez le droit d'interrompre à tout moment votre participation sans avoir à vous justifier et sans que cela n'influence la qualité des soins médicaux qui vous seront prodigués.

QUEL EST LE BUT DE CETTE RECHERCHE ? QUEL EST SON DEROULEMENT GENERAL ?

L'objectif de cette étude est de tester l'efficacité et la tolérance du ponatinib en prévention de la rechute post-allogreffe chez des patients atteints de LAM avec une mutation du gène FLT3 dite FLT3-ITD. L'objectif principal est le calcul du nombre de rechute à 2 ans post-greffe, en espérant diminuer cette incidence de 15% en comparaison des taux actuels observés qui sont de l'ordre de 30%. Nous espérons donc n'observer qu'environ 15% de rechutes post-allogreffe sur l'ensemble des patients traités dans l'étude avec du ponatinib administré pendant un an en maintenance post allogreffe.

La mutation activatrice FLT3-ITD est retrouvée chez environ 20 à 30% des patients atteints de LAM. Elle est associée à un risque accru de rechute. Le médicament ponatinib est un nouveau produit qui bloque certaines protéines dérégulées à cause de mutations anormales de gènes dans les cellules leucémiques. La mutation activatrice FLT3-ITD est ainsi responsable de la croissance et de la prolifération des cellules leucémiques et peut être bloquée par un anti-FLT3 dont le ponatinib.

Pour que vous puissiez participer à cette étude, il faut donc que la mutation FLT3-ITD ait pu être détectée dans vos cellules leucémiques au moment du diagnostic de la maladie.

Le ponatinib a reçu une autorisation de mise sur le marché par les différentes autorités de santé. Il est indiqué dans le traitement de deux types de leucémies associés à la présence d'un chromosome anomal, appelé chromosome Philadelphie (Ph+) : la leucémie myéloide chronique (LMC) et la leucémie aigue lymphoblastique (LAL Ph+). En effet, le ponatinib est aussi un médicament anti-chromosome Philadelphie. C'est donc un médicament déjà connu et déjà utilisé par votre médecin.

A l'heure actuelle, il n'y a pas de traitement standard de maintenance pour les patients porteurs de LAM avec mutation FLT3-ITD en post-allogreffe. Néanmoins, les recommandations du groupe francophone de greffe de moelle (SFGM-TC) est de proposer systématiquement un anti-FLT3 en post-greffe chez ces patients. Un certain nombre de publications médicales ont déjà rapporté des résultats prometteurs avec des anti-FLT3 de première génération en prévention de la rechute post-allogreffe. Le ponatinib est un anti-FLT3 de deuxième génération dont l'activité anti-leucémique testée in vitro semble plus importante que les anti-FLT3 de 1 ère génération et donc il semble intéressant de tester ce médicament en post-greffe même si les données bibliographiques le concernant dans cette indication ne sont pas très robustes.

Puisque l'adjonction du ponatinib en post greffe n'a pas encore été testée, il semble donc intéressant de conduire une évaluation précise de son administration et de son efficacité en maintenance post-allogreffe chez des patients porteurs de LAM FLT3-ITD positive. C'est le but de ce protocole.

Vous débuterez un traitement par ponatinib à la dose de 30 mg/jour en une prise par jour et par voie orale (comprimé) à partir de la fin du deuxième mois par rapport au jour de votre greffe (Jour +60) et ce pour une durée de 1 an au total. Dans cette étude, la dose de médicament ponatinib pourra être diminuée à 15 mg/j en cas d'effets secondaires, voire complétement interrompu si les effets secondaires sont trop graves.

Il n'est pas démontré aujourd'hui qu'un traitement de maintenance supérieur à un an soit bénéfique pour les patients, c'est pourquoi le ponatinib ne sera administré que pour une durée totale de un an.

Le ponatinib vous sera remis pour une durée déterminée lors des visites protocolaires. Vous serez dans l'obligation de rapporter lors des visites suivantes les boites vides de ponatinib pour s'assurer que vous prenez bien votre médicament.

Soixante-dix-sept patients seront inclus au total dans cette étude. La période d'inclusion sera de 2 ans et le suivi par patient de deux ans également. L'étude devrait donc durer 4 ans au total.
Si le nombre suffisant de patients ayant débuté le ponatinib a été atteint, vous pourriez finalement ne pas être inclus(e) dans l'étude bien qu'ayant signé un consentement lors de la pré-sélection. Dans ce cas précis, vous ne serez pas suivi(e) dans le cadre de l'étude et les données vous concernant seront détruites. Cela ne portera en aucun cas préjudice à la qualité de votre prise en charge médicale.

QU'ARRIVERA-T-IL PENDANT LA RECHERCHE ? QU'AUREZ-VOUS A FAIRE ?

Votre participation à cette étude est volontaire. Vous ne serez en aucun cas pénalisé en cas de refus de participer, vous serez pris en charge alors comme tout patient allogreffé.

Votre participation éventuelle à cette recherche durera deux ans à partir du premier jour de la greffe.

La greffe allogénique:

Le déroulement de la greffe, ses objectifs et ses complications possibles vous ont été expliqués par votre médecin.

Dans ce protocole, la durée d'hospitalisation pour la greffe, le nombre de consultations médicales, le type d'examens et de prélèvements sanguins sont les mêmes que pour un patient qui bénéficie d'une greffe « hors étude ».

Visites et Procédures de l'étude :

Visites de Pré-sélection

Deux visites de pré-sélection seront conduites par votre médecin dans le mois précédent l'allogreffe :

-une première consistant à vérifier que vous pouvez bien participer à l'étude. On vous remettra l'ensemble des informations liées à l'étude, ceci afin de vous permettre de considérer votre participation au protocole.

-une deuxième, quelque temps après, au cours de laquelle vous signerez votre consentement informé de participation si vous êtes volontaire pour participer.

Visite de sélection définitive

Elle a lieu après la greffe entre le Jour +45 et +59 post-greffe.

Apres avoir signé le consentement, il vous sera demande de vous soumettre à certaines évaluations et procédures en post-greffe, afin de vérifier si vous pouvez participer définitivement à l'étude. Ces tests et examens font partie le plus souvent des soins habituels délivrés en post-greffe. Si certains examens ont été récemment réalisés (notamment une ponction de moelle osseuse), il ne sera pas utile de les refaire.

Si vous ne remplissez pas les critères d'inclusion du protocole, vous serez alors exclu de l'étude et ne recevrez pas le ponatinib. Vous continuerez dans ce cas-là à recevoir les soins habituels requis lors de la période post-greffe.

Les examens permettant la sélection définitive pour l'étude sont les suivants :

- Examen de vos antécédents médicaux, de votre état de sante actuel, recensement des traitements actuels ou que vous avez reçus dans les 28 jours avant la première prise du ponatinib.
- Examen clinique qui inclut les éléments suivants : température, poids, taille, signes vitaux (tension artérielle, fréquence cardiaque et fréquence respiratoire).
- Radiographie du thorax.
- Electrocardiogramme (ECG), qui enregistre l'activité électrique du cœur.
- Des échantillons sanguins seront aussi prélevés pour vérifier la numération globulaire (nombre de globules blancs, globules rouges et plaquettes dans le sang), la coagulation et la chimie sanguine (pour tester la fonction rénale, la fonction hépatique, la fonction pancréatique et doser les minéraux).
- Dans les 28 jours précédant le début du ponatinib, une ponction de moelle osseuse sera réalisée pour évaluer votre maladie. Cette ponction est pratiquée après anesthésie locale à l'aide d'un trocart fixé dans le sternum ou l'os iliaque.
- Si vous êtes une femme en âge de procréer, vous devrez effectuer un test de grossesse urinaire ou sanguin, dans les 72 heures qui précèdent le début du ponatinib; ce test doit être négatif pour participer à l'étude.
- Pendant cette période de sélection il pourra s'avérer que vous ne remplissez pas tous les critères de sélection. Dans ce cas vous serez informe(e) qu'il ne vous sera pas possible de participer à cette étude.

Evaluation au cours de l'étude :

Les procédures de surveillance sont celles habituellement appliquées chez des patients allogreffés.

Les examens de surveillance suivants seront réalisés régulièrement durant les 3 premiers mois puis à 6, 9, 12 mois après le début de la prise du ponatinib puis à la fin de l'étude (à 2 ans de la greffe):

- Un électrocardiogramme (ECG), une radio de thorax.
- Des échantillons sanguins pour vérifier la numération globulaire, la coagulation et la chimie sanguine. On surveille également l'absence d'infection par le virus de l'hépatite B car le ponatinib peut favoriser très rarement des hépatites de type B.
- Une échographie cardiaque et des explorations respiratoires fonctionnelles de contrôle sont réalisées systématiquement à 6 mois, 1 an et 2 ans après la greffe.
- Une ponction de moelle osseuse sera réalisée pour évaluer votre maladie à 1 an et 2 ans post-greffe ou en cas de suspicion de rechute.

Voici un tableau résumant les examens et visites réalisés au cours du protocole : J=Jour, JO=jour de la greffe

Activities	J-30 -7 (Pre-inclusion visit)	J+30/+60 (Inclusion visit)	Mois 1 ponatinib	Mois 2 ponatinib	Mois 3 ponatinib	Mois +6 /+9/+12 ponatinib	Fin de l'étude
Information du patient	X						
Signature Consentement		X					
Inclusion par fax / email		X					
Antécédents médicaux		X					
Examen Clinique, état général, médicaments en cours		X	X	X	X	X	X
Electrocardiogramme et mesure du QTc		x	X	X	X	X	X
Echographie cardiaque Explorations respiratoires	x					Mois 6, 12 et 24	x
Radio de thorax	x					Mois 6, 12 et 24	X
Analysis biochimiques		X	X	X	X	X	X
Sérologie Hépatite B	x	x			x	x	
Efficacité du ponatinib et toxicité			X	X	X	X	x
Compliance au ponatinib			X	X	X	X	
Evènements indésirables			X	X	X	X	X
Ponction de moelle (myélogramme) *en cas de suspicion de rechute		x	*	*	*	* + mois 12 et 24	* +24 mois greffe

QUELS SONT LES RISQUES ASSOCIES A LA PRISE DU PONATINIB ?

Le ponatinib est un médicament déjà commercialisé pour le traitement de patients atteints de leucémies associées à la présence d'un chromosome philadelphie (Ph+) : leucémie myéloide chronique (LMC) et leucémie lymphoblastique aigue (LAL ph+). En effet le ponatinib qui a des propriétés anti-FLT3 a aussi des propriétés anti-chromosome Philadelphie.

Les effets indésirables du ponatinib ont été identifiés durant un essai international ayant porté sur 449 patients atteints de LMC et de LAL Ph+.

Les effets indésirables graves les plus fréquents > 2 % (fréquences des effets apparus sous traitement) étaient les suivants : pneumonie (7,1 %), pancréatite (5,8 %), fièvre (5,0 %), douleurs abdominales (5,0 %), infarctus du myocarde (4,0 %), fibrillation auriculaire (4,0 %), artériopathie oblitérante périphérique (thrombose des artères des jambes) (3,8 %), anémie (3,6 %), angine de poitrine (3,3 %), diminution du nombre de plaquettes sanguines (3,1 %), neutropénie (baisse des globules blancs) fébrile (2,9 %), hypertension (2,7 %), insuffisance cardiaque (2,4 %), accident vasculaire cérébral (2,4 %), maladie coronarienne (2,4 %), sepsis (infection grave) (2,2 %) et augmentation du taux de lipase (pancréatite) (2,0 %).

Des effets indésirables artériels occlusifs cardiovasculaires, cérébro-vasculaires et vasculaires périphériques graves sont survenus respectivement chez 9 %, 7 % et 7 % des patients traités par ponatinib. Des effets indésirables veineux occlusifs graves se sont produits chez 5 % des patients.

Des effets indésirables artériels occlusifs cardiovasculaires, cérébro-vasculaires et vasculaires périphériques (graves ou non graves) sont survenus respectivement chez 13 %, 9 % et 9 % des patients traités par ponatinib. Des thromboembolies veineuses sont apparues chez 6 % des patients. Aucun événement veineux occlusif d'issue fatale n'a été rapporté.

Les événements artériels ou veineux sont apparus chez des patients avec ou sans facteurs de risque cardiovasculaire, y compris chez des patients âgés de 50 ans ou moins. Les événements artériels occlusifs étaient plus fréquents chez les patients plus âgés et chez ceux présentant des antécédents d'ischémie, d'hypertension, de diabète ou d'hyperlipidémie.

L'incidence des événements indésirables associés au traitement et ayant entraîné son interruption était comprise entre 9 et 17% des patients en fonction de la maladie (LMC ou LAL Ph+).

La myélosuppression (baisse des globules du sang) a été fréquemment rapportée dans toutes les populations de patients. Une myélosuppression a été rapportée chez les patients dont les constantes biologiques initiales étaient normales, ainsi que chez ceux ayant des anomalies biologiques préexistantes. L'interruption du traitement due à une myélosuppression n'était pas fréquente (baisse de plaquettes 4 %, baisse de globules blancs et globules rouges < 1 % pour chacune).

Des cas de réactivation du virus de l'hépatite B ont été rapportés, parfois graves. Nous vérifierons votre sérologie hépatite B avant le début du traitement puis au cours du traitement par ponatinib.

En cas d'effets secondaires graves dus au ponatinib, votre médecin devra interrompre votre traitement jusqu'à amélioration. Lorsque les effets secondaires auront disparu ou diminué, votre médecin décidera si la reprise du ponatinib à une plus faible dose est justifiée ou s'il est préférable que vous arrêtiez définitivement le traitement. Comme les effets du ponatinib

pris avec d'autres médicaments ne sont pas tous connus, en particulier après allogreffe, vous devrez pendant l'étude informer votre médecin, d'une part, de la prise de nouveaux médicaments quels qu'ils soient, et d'autre part de la survenue de symptômes inhabituels. Pendant l'étude clinique, vous serez informé des nouveaux effets secondaires survenus chez les patients ou des éléments importants susceptibles d'affecter votre santé. Vous devrez alors éventuellement signer un nouveau formulaire de consentement, indiquant que vous avez été informé de nouveaux éléments associés à cette étude clinique.

Risque relatif à une grossesse :

Le ponatinib peut affecter le développement du foetus ou du nourrisson. Il convient aux femmes en âge de procréer et aux hommes traités par ponatinib de respecter certaines règles.

Si vous êtes une femme en âge de procréer:
Un test de grossesse sera réalisé dans les 72 heures avant la première prise du ponatinib. C test doit être négatif pour participer à l'étude. Vous devrez ensuite utiliser une méthode de contraception efficace jusqu'à trois mois après l'arrêt d'administration du ponatinib. Si vous tombez enceinte pendant l'étude ou dans les 3 mois suivant la fin du traitement, il faudra en informer immédiatement votre médecin. Vous devrez alors arrêter l'étude pour des raisons de sécurité. L'allaitement est également interdit pendant toute la durée de l'étude.

Si vous êtes un homme :
Si votre épouse ou partenaire est en âge de procréer, vous devez accepter d'utiliser un moyen de contraception efficace jusqu'à trois mois après l'arrêt du ponatinib. Si votre épouse ou partenaire pense qu'elle est enceinte pendant votre participation à l'étude ou dans les 3 mois suivant la fin du traitement, vous devez en informer immédiatement votre médecin.

QUELS SONT LES BENEFICES QUE VOUS POUVEZ ESPERER ?

La greffe allogénique est utilisée depuis maintenant 60 ans dans le traitement des patients souffrant d'hémopathies malignes. Cette technique est considérée actuellement comme celle pouvant apporter la meilleure efficacité dans le contrôle et l'élimination des cellules tumorales dans votre maladie. Néanmoins nous sommes encore confrontés à des rechutes post-greffe, en particulier chez les patients FLT3-IDT positifs. Des stratégies de prévention de la rechute sont aujourd'hui possible en ciblant les mutations de gènes présentes au sein de la cellule leucémique. L'objectif ici est de pouvoir permettre d'éviter les rechutes après la greffe en utilisant le ponatibib, un traitement anti-FLT3-ITD.
Les bénéfices individuels pour chaque patient peuvent donc être moins de récidive de la maladie, et donc moins d'hospitalisations, de transfusions, de recours à des chimiothérapies de rattrapage.
En ce qui concerne les bénéfices collectifs, on s'attend également à diminuer les rechutes avec un bénéfice important en termes de cout relatif aux différentes prises en charge nécessaires en cas de rechute.

QUELLES SONT LES ALTERNATIVES ?

En cas de refus de participer au protocole, vous recevrez une procédure de greffe classique sans stratégie de prévention de la rechute par ponatinib.

QUE SE PASSERA-T-IL A LA FIN DE LA RECHERCHE, SI LA RECHERCHE S'ARRETE OU SI VOUS DECIDEZ D'INTERROMPRE VOTRE PARTICIPATION ?

Votre médecin pourra décider de vous faire arrêter l'étude si:

- Pour une raison quelconque, vous revenez sur votre consentement,
- Pour une raison quelconque, vous ne pouvez pas suivre les obligations de l'étude comme se rendre régulièrement aux consultations planifiées, respecter les prises du médicament ou faire pratiquer les examens requis par l'étude.
- Vous prenez un des médicaments interdits mentionnés dans le protocole de l'étude, sans l'accord du médecin responsable de l'étude,
- Le médecin responsable pense qu'il en va de votre intérêt,
- Le médicament ou les examens de l'étude se révélaient dangereux ou inefficaces.

- Toute autre raison imprévisible peut également imposer l'arrêt de votre participation à cette étude clinique.
- L'étude peut être arrêtée à tout moment également par les autorités de santé ou du fait du promoteur, le CH de Versailles : si un élément nouveau survient, le médecin-investigateur en sera informé et il vous transmettra alors les éléments susceptibles de modifier votre participation.

Quelle que soit la raison de cette interruption, le médecin-investigateur vous informera alors des mesures à suivre. Dans ce cas, votre suivi de greffe sera celui prévu pour tout patient greffé. Dans tous les cas, la qualité de votre prise en charge ne sera pas diminuée.

AUREZ-VOUS DES FRAIS SUPPLEMENTAIRES ?

Votre participation à cette recherche n'engendrera pour vous aucun frais supplémentaire par rapport à ceux que vous auriez dans la prise en charge habituelle de votre maladie.

QUELS SONT VOS DROITS PENDANT LA RECHERCHE ?

❖ SECRET PROFESSIONNEL

Le personnel impliqué dans la recherche est soumis au secret professionnel, tout comme votre médecin traitant.

Sauf avis contraire de votre part, votre médecin traitant sera informé de votre participation à cette étude.

❖ ACCES AUX DONNEES VOUS CONCERNANT - TRAITEMENT DES DONNEES

Dans le cadre de cette recherche, un traitement informatique de vos données personnelles va être mis en œuvre : cela permettra d'analyser les résultats de la recherche et de remplir l'objectif de la recherche.

Pour cela, les données médicales vous concernant, seront transmises au Promoteur de la recherche (CH de Versailles) ou aux personnes ou sociétés agissant pour son compte. Ces données seront identifiées par un numéro de code et vos initiales. Ces données seront susceptibles d'être exploitées dans le cadre de publications ou de communications ; dans ce cas, votre anonymat sera préservé.

Ces données pourront également, dans des conditions assurant leur confidentialité, être transmises aux autorités sanitaires habilitées. Conformément aux dispositions de la loi relative à l'informatique aux fichiers et aux libertés (loi modifiée du 6 janvier 1978), vous disposez d'un droit d'accès et de rectification. 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.

Ces droits s'exercent auprès du médecin-investigateur qui vous suit dans le cadre de la recherche et qui connaît votre identité.

Vous pouvez également accéder directement ou par l'intermédiaire d'un médecin de votre choix à l'ensemble de vos données médicales en application des dispositions de l'article L 1111-7 du Code de la Santé Publique.

❖ **ACCES AUX RESULTATS GLOBAUX DE LA RECHERCHE**

A la fin de la recherche biomédicale, et à votre demande, vous pourrez être informé(e) par le médecin-investigateur des résultats globaux de cette recherche (dès qu'ils seront disponibles).

QUELLES SONT VOS OBLIGATIONS PENDANT LA RECHERCHE ?

❖ **VOS OBLIGATIONS**

IL VOUS SERA DEMANDE :

D'informer votre médecin investigateur de tous les médicaments que vous prenez.

De prendre correctement le médicament à l'étude et de ramener à la pharmacie qui le délivre les boites vides afin de s'assurer de votre bonne compliance.

D'informer votre médecin immédiatement de tout effet indésirable éventuellement rencontré au cours de votre participation à la recherche.

De vous rendre aux visites prévues.

De réaliser les examens requis par l'étude.

❖ **PROTECTION SOCIALE**

Pour pouvoir participer à cette recherche vous devez être affilié(e) ou bénéficier d'un régime de sécurité sociale *(CMU acceptée)*.

❖ **MODALITES DE PARTICIPATION A UNE AUTRE RECHERCHE**

Vous ne pourrez participer à aucune autre recherche biomédicale pendant toute la durée de votre participation à cette étude, à l'exception d'études dites « non interventionnelles », ne modifiant pas le suivi habituel de la greffe et impliquant ou non des prélèvements biologiques ou tissulaires.

LE CADRE LEGAL ET REGLEMENTAIRE

Cette recherche est conforme :

- Aux articles L. 1121-1 à L. 1126-12 du code de la santé publique relatifs aux recherches impliquant la personne humaine

- A la loi « Informatique et Libertés » du 6 janvier 1978 modifiée.

Vous pouvez retrouver tous ces textes sur le site http://www.legifrance.gouv.fr

Conformément aux dispositions légales :

Le CH de Versailles organise cette recherche en tant que « promoteur ». Il a souscrit un contrat d'assurance garantissant sa responsabilité civile et celle de tout intervenant auprès de la SHAM (police d'assurance n° 109644).

Cette recherche a reçu l'avis favorable du Comité de Protection de Personnes Nord-Ouest III le 04 mai 2018 La recherche a aussi reçu l'autorisation de l'ANSM (Agence Nationale de Sécurité du Médicament et des Produits de Santé), le 20 mars 2018.

EN RESUME

Votre participation à cette recherche est libre. Vous pouvez refuser de participer à cette recherche.

De plus, vous pouvez à tout moment vous retirer de cette recherche, sans préjudice.

Si vous décidez de ne pas participer à l'étude ou si vous décidez d'arrêter votre participation pendant la recherche :

- cela n'aura aucune conséquence sur la qualité des soins qui vous seront donnés
- vous devez simplement en informer votre médecin-investigateur.

Lorsque vous aurez lu cette note d'information et obtenu les réponses aux questions que vous vous posez en interrogeant le médecin-investigateur, il vous sera proposé, si vous en êtes d'accord, de donner votre consentement écrit en signant le formulaire préparé à cet effet.

Votre participation à la recherche, au cas où vous donneriez votre accord, ne pourra vous être confirmée qu'à la condition que vous remplissiez tous les critères d'inclusion pour participer à cette recherche.

Si le nombre de patients prévus dans l'étude a été atteint, vous pourrez finalement ne pas être inclus(e) dans l'étude même après avoir signé votre consentement. Dans ce cas précis, vous ne serez plus suivi(e) dans le cadre de l'étude et les données vous concernant ainsi que vos échantillons sanguins le cas échéant seront détruits. Cela ne portera, en aucun cas, préjudice sur la qualité de votre prise en charge médicale.

Vous pouvez prendre votre temps avant de nous donner votre réponse. Vous avez 10 jours pour prendre votre décision, à partir de la remise de cette note d'information.

Au cours de ce délai de réflexion, vous pouvez bien entendu continuer par téléphone à poser toutes les questions que vous souhaitez à votre médecin-investigateur (Dr/Pr…….. tél……..).

Nous vous prions d'agréer, Madame, Monsieur, l'expression de nos sentiments les plus respectueux.

Pr CHEVALLIER Patrice, médecin coordonnateur et investigateur principal,

et toute l'équipe médicale en charge de cette recherche

APPENDIX 8 : FORMULAIRE DE RECUEIL DE CONSENTEMENT DES PATIENTS

	FORMULAIRE DE CONSENTEMENT POUR PARTICIPATION A UNE RECHERCHE INTERVENTIONNELLE
Version	Version n°1. 2 – 27/04/2018
Protocole	"Phase 2 study of Ponatinib (Iclusig) for prevention of relapse after allogeneic stem cell transplantation (allo-SCT) in FLT3-ITD AML patients: the PONALLO trial." « Etude de Phase 2 testant le Ponatinib (Iclusig) en prévention de la rechute post-allogreffe pour des patients atteints de leucémie aigue myéloblastique FLT3-ITD positive : Etude PONALLO."

Je soussigné(e)

M^{e}, M. *(rayer les mentions inutiles*) (*prénom*, NOM) ……

Date de naissance : …../……/……..

accepte librement et volontairement de participer à la recherche référencée ci-dessus, coordonnée par le Professeur Chevallier et organisée par le CH de Versailles, promoteur de la recherche.

Etant entendu que :

- Le médecin qui m'a informé(e) et a répondu clairement à toutes mes questions, m'a précisé que ma participation est libre et que je peux me retirer de la recherche à tout moment.
- J'atteste ne pas faire l'objet de mesure de protection (tutelle, curatelle, sauvegarde de justice), en outre je confirme être affilié(e) ou bénéficier d'un régime de sécurité sociale.
- Il m'a été préalablement remis une note d'information sur cette recherche précisant son but, sa méthodologie, ses bénéfices attendus et ses risques prévisibles.
- Je pourrai avoir communication par le médecin, au cours ou à l'issue de la recherche, des informations qu'il détient concernant ma santé.
- Si le nombre de patients prévus dans l'étude a été atteint, je pourrais finalement ne pas être inclus(e) dans l'étude bien qu'ayant signé un consentement. Dans ce cas précis, je ne serai plus suivi(e) dans le cadre de l'étude et les données me concernant ainsi que les échantillons sanguins le cas échéant seront détruits. Cela ne portera, en aucun cas, préjudice sur la qualité de ma prise en charge médicale.
- Je suis parfaitement conscient(e) que je peux retirer à tout moment mon consentement à ma participation à cette recherche et cela quelles que soient mes raisons et sans supporter aucune responsabilité, mais je m'engage dans ce cas à en informer le médecin. Le fait de ne plus participer à cette recherche ne portera pas atteinte à mes relations avec ce médecin, ni à la qualité des soins qui me seront donnés.
- J'accepte que mon médecin traitant soit informé de ma participation à la recherche :

  ☐ Oui, j'accepte ☐ Non, je refuse
- Je pourrai à tout moment demander des informations complémentaires au médecin.
- Si je le souhaite, à son terme, je serai informé(e) par le médecin des résultats globaux de cette recherche.
- Mon consentement ne décharge en rien le médecin et le promoteur de l'ensemble de leurs responsabilités et je conserve tous mes droits garantis par la loi.

- Je ne pourrai pas participer à une autre recherche biomédicale pendant toute ma participation à cette recherche, et jusqu'à 30 jours après sa fin.
- J'accepte que les données enregistrées à l'occasion de cette recherche puissent faire l'objet d'un traitement informatisé par le promoteur ou pour son compte. J'ai bien noté que le droit d'accès prévu par la CNIL (loi du 6 janvier 1978 modifiée relative à l'informatique, aux fichiers et aux libertés (art. 39)) s'exerce à tout moment auprès du médecin qui me suit dans le cadre de la recherche et qui connaît mon identité. Je pourrai exercer mon droit de rectification et d'opposition auprès de ce même médecin, qui en informera le promoteur de la recherche. Mes données resteront confidentielles.
- J'accepte que les personnes en charge du suivi de la recherche aient accès aux données de mon dossier médical.
- J'accepte l'utilisation de mes données à des fins de communications / publications sous format anonyme.

Date :	*Le cas échéant* : Attestation du consentement en cas d'impossibilité d'expression écrite de la personne qui se prête à la recherche biomédicale (précision du titre de la personne)	
Signature du patient :	Date : Prénom NOM :	Signature :

Signature du médecin qui atteste avoir pleinement expliqué à la personne signataire le but, les modalités ainsi que les risques potentiels de la recherche.	
Date :	NOM et Signature :

Ce document est à réaliser en 2 exemplaires originaux : le premier doit être conservé par l'investigateur et le deuxième est remis à la personne donnant son consentement. En cas de duplicata, l'original est conservé par l'investigateur et une copie est remise à la personne ayant donné son consentement.