LAM PONATINIB - (dernière mise à jour : 22/10/2019)

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Informations générales

Titre de l'étude : A Phase I - II Study to Assess Safety and Efficacy of the Combination of Ponatinib With High or Intermediate-Dose Cytarabine as Consolidation Therapy for Patients With Intermediate-Risk Cytogenetic FLT3-ITD AML in First Complete Remission

Traitement :

Type d'étude : Ciblage moléculaire / Innovation thérapeutique

Phase : I/II **Stade** : NA **Ligne(s)** :

Schéma : This project is part of a joint ALFA and GOELAM strategy aiming to improve the survival of patients with newly diagnosed Acute Myeloid Leukemia (AML) aged 18-70 years. The basis of this strategy is to evaluate intensified conventional chemotherapy and targeted drugs in selected disease-risk subgroups of adult patients with non promyelocytic AML. Participation will be proposed to almost all adult patients in France aged 18-70 years and diagnosed with AML.

FLT3 genetic alterations include FLT3 somatic point mutations within the second tyrosine kinase domain and internal duplications of the juxta-membrane domain. This alteration is refered to as FLT3-ITD. The FLT3-ITD mutation is found in around 30% of 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% (Schlenk et al. N Engl J Med 2008). More recently, the prognostic relevance of FLT3-ITD has been studied in the context of integrated genetic profiling. This confirmed the genetic complexity of AML and also 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%) (Patel JP et al. N Engl J Med 2012). However, FLT3-ITD was not a predictor of response to induction therapy, allowing the introduction of targeted therapies after the induction course.

Several FLT3 inhibitors have been evaluated or are currently being tested in the setting of relapsing AML. In most trials to date, 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 likely present a major limitation in evaluating AC220 combined 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 inhibits SRC (IC50: 5.4 nM) and members of the VEGFR, FGFR, and PDGFR families of receptor tyrosine kinases (O'Hare T, Cancer Cell 2009). Despite low activity against FLT3 based on the IC50 value (FLT3 IC50: 12.6 nM compared to BCR IC50: 0.37 nM), ponatinib has recently been reported to have significant cellular activity against the MV4-11 cell line which harbors an FLT3-ITD activating mutation. Ponatinib-induced apoptosis was maximal at 10 nM in vitro and a single dose of 5 and 10 mg/kg had a strong inhibitory effect in vivo in mice bearing MV4-11 xenografts. Primary blast cells from 4 FLT3-ITD AML patients were also tested and ponatinib reduced their viability (IC50: 4 nM) whereas no activity was shown on FLT3-ITD-negative blast cells (Gozgit JM et al. Mol Cancer Ther 2011).

Preliminary data from the phase I clinical trial showed that 15 mg ponatinib was associated with a Cmax of 51.1 nM. Cmax was increased to 111 nM and 149 nM in the 30 mg and 45 mg cohorts respectively. The trough concentrations were 55.3 nM and 61.9 nM for the 30 mg and 45 mg doses respectively (Ariad clinical investigator's brochure, version 3). Results from the ongoing phase II trial in CML patients suggest that the hematological toxicity profile of ponatinib is comparable with that of nilotinib or dasatinib, both of which have been successfully combined with conventional chemotherapy.

Investigators thus aim to combine ponatinib with cytarabine in FLT3-ITD AML patients in first complete remission.

Intervention: Drug: Ponatinib and Cytarabine

Prospective, non-randomized, open-label, multicenter, dose-escalation phase I-II trial; an adaptive Bayesian logistic regression dose-escalation model incorporating escalation with overdose control will be used (Babb 1998, Tighiouart 2005). Each cohort will consist of 3 evaluable patients

Study Arms:Experimental: Ponatinib arm
dose-escalation Arm _ 15, 30, 45mg Ponatinib per day. Each cohort will consist of 3 evaluable patients

Current primary outcome:
dose-limiting toxicity (DLT) of ponatinib during consolidation 1 with HDAC or IDAC [Time Frame: 12 months]
assess the safety of increased doses of ponatinib in combination with high or intermediate -dose cytarabine in AML FLT3-ITD patients in first complete remission

Current secondary outcomes:
- Overall survival [Time Frame: 5 years]
To determine disease-free survival from achievement of first complete remission
- Relapse-free survival [Time Frame: 5 years]
To determine overall survival from achievement of first complete remission
- Event-free survival [Time Frame: 5 years]
To determine overall survival from diagnosis
- Minimal residual disease based on FLT3-ITD quantification, WT1 expression and/or NPM1 mutation quantification [Time Frame: 18 months]
To study minimal residual disease after induction and consolidation courses based on the quantification of the FLT3-ITD signal and /or WT1, NPM if available
- relationship between minimal residual disease and outcome [Time Frame: 18 months]
To study the relationship between minimal residual disease and outcome
- To study ponatinib resistance mechanisms [Time Frame: 18 months]
To assess FLT3-ITD mutant before and after ponatinib treatment

Spécialités / Localisations

Spécialité n°1 : Tissus lymphoïde, hématopoïétique et apparentés

CIM10 - Localisation n°1 : **C92** - Leucémie myéloïde

Critères

Critères d'inclusion : - a. Patients aged 18 to 55-60 years: Cohort A b. Patients aged 55-60 to 70 years: Cohort B
- Signed informed consent
- Acute myeloid leukemia in first complete remission
- Platelets >= 100 Giga/l; Neutrophils >= 1 Giga/l
- Intermediate risk karyotype with FLT3-ITD activating mutant detected at diagnosis (mutant FLT3/wild-type allelic ratio higher than 10%) (appendix 16)
- Induction with intensive chemotherapy, dose dense sequential induction or 3 + 7 like regimen (daunorubicin or idarubicin) for Cohort A and inclusion in the ALFA backbone for cohort B.
- Pancreatic functions within the normal range
- AST or ALT less or equal to 2.5 fold upper normal range, bilirubin less or equal to 1.5 fold upper normal range
- Serum creatinine less or equal to 1.5 fold upper normal range
- Two planned consolidation courses with high-dose cytarabine (HDAC, Cohort A) or intermediate dose cytarabine (IDAC, Cohort B).

Critères de non-inclusion : - Acute promyelocytic leukemia
- Transformation of myeloproliferative or myelodysplastic syndromes
- Known central nervous system involvement

- Uncontrolled bacterial, viral or fungal infection
- Other active malignancy
- revious episode of pancreatitis
- Hypertriglyceridemia > 4.5 g/L
- Lipase > 1.5 × ULN, amylase > 1.5 x ULN not related to leukemia
- QTc > 470 ms (Bazett formula, see Appendix 1)
- Patients at high or very high risk of cardiovascular disease with any of the following f) 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.
> 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 i) Familial dysplipidemia. j) Taking medications that are known to be associated with Torsades de Pointes (see Appendix 11)

Informations promoteur

Nom du promoteur : CH VERSAILLES

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Statut de l'essai : CLOS

Liens utiles

ClinicalTrials (anglais) : https://clinicaltrials.gov/ct2/show/record/NCT02428543