Intergroup ALFA/GOELAMS Randomized Phase II Trial of Lirilumab as Maintenance Treatment in Elderly Patients with Acute Myeloid Leukemia (EffiKIR Trial)

ASCO 2013
Abstract #TPS3117
Board #23

N. Vey[1], H. Dombret[2], N. Ifrah[3], A. Pigneux[4], C. Gardin[5], M. Buyse[6], P. Andre[7], A. Tirouvanziam-Martin[7], R. Zerbib[7], R. Buffet[7], and M. Rozencweig[7]

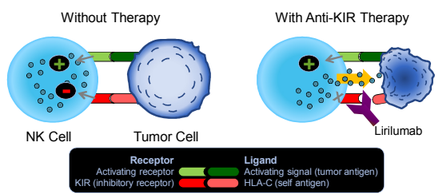
1- Institut Paoli-Calmettes, Marseilles, France; 2 - Hopital Saint Louis, Paris, France; 3- CHU Angers, France; 4- CHU Bordeaux, France; 5- Hopital Avicenne, Bobigny, France; 6- IDDI, Brussels, Belgium; 7- Innate Pharma, Marseille, France.

Background

New Approaches to Maintain Complete Remission in Patients ≥60 years with AML are Urgently Needed

- Median LFS does not exceed 15 months after CR *(1)*
- Long-term survivors are rare

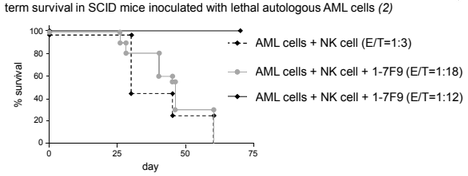
Mechanism of Action: Lirilumab (anti-KIR) blocks an inhibitory signal to NK cells



- NK cell activation is determined by the balance of activating (positive) and inhibitory (negative) receptor stimulation
- Tumor cells are able to evade innate immunity through the interaction of KIR with HLA-C
- By blocking this interaction, lirilumab facilitates the activation of NK cells and subsequent apoptosis of the tumor cell

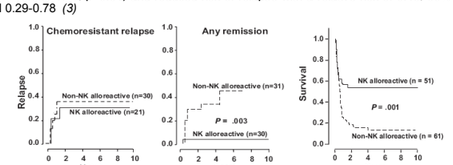
In vivo Efficacy of Anti-KIR

- Anti-KIR blockade by IPH2101 (a first generation of anti-KIR antibody) resulted in long-term survival in SCID mice inoculated with lethal autologous AML cells *(2)*



Haploidentical Donors in Hematopoietic Cell Transplantation

- Lack of KIR-HLA class I interactions has been associated with potent NK-mediated antitumor efficacy and increased survival in patients with acute myeloid leukemia (AML) upon haploidentical stem cell transplantation from KIR-mismatched donors
- AML patients transplanted with KIR mismatched donor NK cells had lower relapse rates (3% versus 47%, p<0.01) and reduced risk of relapse with a relative risk of 0.48, 95% CI 0.29-0.78 *(3)*



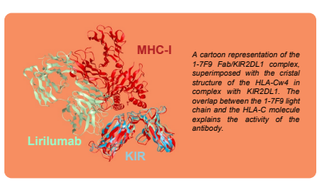
Lessons of allogeneic stem cell transplantation: Importance of the KIR HLA-C mismatch

The benefit of a mismatch between KIRs and their ligands has been documented in AML patients in Complete Response (CR) in the setting of allogeneic stem cell transplantation

The goal of the study is to pharmacologically recapitulate KIR mismatch effect with lirilumab, an anti-KIR blocking mAb, administered in elderly patients with AML in CR not eligible for allogeneic stem cell transplantation

Lirilumab

- Lirilumab (IPH2102/BMS986015) is a fully human monoclonal antibody
- Targets KIR2DL expressed by NK cells (but also targets 2DS)
- Blocks interactions between KIRs and their HLA-C ligands
- Lirilumab is an IgG4 without cytotoxic activity
- Produced in CHO recombinant cells



A cartoon representation of the 1-7F9 Fab/KIR2DL1 complex, superimposed with the cristal structure of the HLA-Cw4 in complex with KIR2DL1. The overlap between the 1-7F9 light chain and the HLA-C molecule explains the activity of the antibody.

Survival in Phase I Trial of Maintenance IPH2101 in Elderly Patients in Complete Remission From AML

- The 6 patients treated at dose levels 1 and 3 mg/kg of IPH2101 (previous hybridoma version of anti-KIR) showed a significantly improved OS compared with the 16 patients treated at lower dose levels(≤ 0.3 mg/kg): 29.7 months compared with 11.8 months, respectively (*P* = .034 by log-rank test); *(4)*

EffiKIR Trial (NCT 01687387)

Design

- Placebo controlled, double-blinded, 1:1:1, randomized, 3 arms
- Elderly AML patients in CR1 not eligible for HST
- 150 patients to be treated for 24 months
  - ✓ Monthly administrations during the whole treatment period
  - ✓ Quarterly clinical follow-up and monthly hematology monitoring after completion of the treatment until relapse
- Designed with ALFA and GOELAMS collaborative groups
  - ✓ Principal Investigator: Norbert Vey, Paoli-Calmettes Institute, Marseille
- Sponsored by Innate-Pharma, Marseille

Endpoints

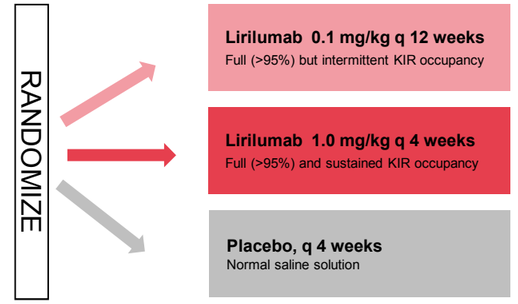
- Primary Endpoint: Leukemia-Free Survival
  - ✓ Calculated from the day of randomization until the occurrence of a relapse or death from any cause
  - ✓ Date of the relapse validated by an Independent Review Committee
  - ✓ Control LFS estimated at 12 months (placebo group) as determined from ALFA /GOELAMS data base
  - ✓ Target LFS of 20 months in lirilumab groups
- Secondary endpoints
  - ✓ Safety (CTCAE v 4.03); safety review by Data and Safety Monitoring Board
  - ✓ Efficacy
    - Time To Relapse, Overall Survival, Leukemia-Specific Survival
  - ✓ Exploratory analyses
    - Pharmacokinetics, KIR occupancy and immunogenicity

Minimization Procedure

- Computerized stochastic minimization according to 4 factors
  - ✓ Center
  - ✓ Primary versus secondary AML
  - ✓ Number of consolidation cycles (1 versus 2)
  - ✓ Cytogenetics (high versus intermediate risk)
    - As defined according to European Leukemia Net *(5)*

Timelines

Recruitment status	Recruiting
Recruitment period	15-18 months
Study start date	October 2012
Estimated completion date	June 2016



Statistical Considerations

- ✓ Primary endpoint: Leukemia-Free Survival (Independent Review Committee)
- ✓ N=50 per arm (100 events) for overall α at 0.05 one-sided and power of 0.80, assuming median LFS of 12 months in the control group vs. 20 months in the treatment groups.

Participants: 42 centers in France

Main Inclusion Criteria

- Primary or secondary AML
- First Complete Response (CR) / Complete Response with incomplete blood count recovery (CRi)
- Induction chemotherapy performed within the previous 6 months
- Consolidation by 1 or 2 cycles of chemotherapy initiated within 3 months following the induction
- Not eligible for an allogeneic HCT
- Age: 60 to 80 years
- ECOG: 0-1
- Recovery from acute toxicity of previous antitumor therapy
- Laboratory values at screening:
  - ✓ Platelets > 75 x 10^9 /l, Neutrophils > 1 x 10^9 /l, Hb ≥ 10 g/dl
  - ✓ Adequate renal and liver function

Main Exclusion Criteria

- Good risk cytogenetics including
  - ✓ Acute Promyelocytic Leukemia with t(15; 17) or its molecular equivalents
  - ✓ Core Binding Factor AML with t(8; 21) or inv(16) or t(16;16) and its molecular equivalents
- Last consolidation completed more than 3 months prior to first dosing
- Insufficient wash-out
  - ✓ ≤ 28 days : chemotherapies, growth factors, systemic corticosteroids
  - ✓ ≤ 2 months: experimental agents
  - ✓ ≤ 3 months : irradiation (except for antalgic intent)
- Autologous or allogeneic hematopoietic cell transplantation, solid organ transplantation
- Auto-immune disease, current active or chronic viral infection, abnormal cardiac status

References

1. Burnett A et al. *J Clin Oncol* 2010; 115: 453;
2. Romagné F et al.. *Blood* 2009; 114: 2667-74
3. Ruggeri L et al.. *Blood*. 2007;110:433-40;
4. Vey N et al. *Blood* 2012; 120: 4317-4323;
5. Döhner H et al.. *Blood* 2010; 115: 453-74.