A Phase I Study of the Anti-Natural Killer Inhibitory Receptor (KIR) Monoclonal Antibody (IPH2101) in Elderly Patients with AML:

Clinical and Immunological Effects of a Single Dose Followed by Repeated Dosing

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Clinical background and rationale

- Prognosis of AML in the elderly is poor:
  - CR rate range between 50%-60%
  - Short CR duration (median 9 months)
  - Survival 5% at 5 years
- Defective NK-cells in AML patients (Costello, Blood 2002; Fauriat, Blood 2007) restored following CR
- Strong evidence for a role of NK-cells against AML blasts (Ruggieri, Science 2002; Miller, Blood 2005)
- NK-cells number and functions are restored 30 days after chemotherapy in patients with AML in CR1 (Olive, ASH 2009, Abst #1653)

Study design (protocol IPH2101-101)

- Open label phase I multicenter study of escalating doses of IPH2101
- Objectives:
  - To determine MTD
  - To assess KIR occupancy (target: >90% saturation for 4 weeks in the absence of DLT)
  - To evaluate PK/PD
- Eligibility:
  - Patient aged $\geq$ 60 years and $\leq$ 80 years
  - AML excluding promyelocytic and CBF AMLs
  - First CR following 1 or 2 cycles of induction chemotherapy, and following 1 to 6 cycles of consolidation chemotherapy
  - Written informed consent
- Extension trial (protocol IPH2101-102)
  - Patients still in CR who tolerated IPH2101 single dose
  - Repeated dosing of IPH2101 (every 4 weeks for 6 cycles)

Patient characteristics

Sex (M/F)		14/9
Age (years)	Median Min-Max	71 61-79
Duration of disease (wks)	Median Min-Max	25 16-56
Duration from CR to inclusion (wks)	Median Min-Max	20 2-51
Last chemotherapy (weeks)	Median Min-Max	9 6-21
Karyotyping	Normal Complex Chr 5/7 abn. Other abn. NE	14 3 2 3 1
Absolute NK (number/µl)	Median Min-Max	124 20-843
IP2101^{+} NK cells (%)	Median Min-Max	35.1 8.1- 54.1

Results : dose escalation

Dose Level	Dose (mg/kg)	No. of Patients
1	0.0003	n=3
2	0.003	n=3
3	0.015	n=3
4	0.075	n=4*
5	0.3	n=4 *
6	1	n=3
7	3	n=3

Study completed :

23 patients included in 7 dose-level cohorts

* 2 patients were replaced

- one at 0.075mg/kg dose level relapse before the 4 weeks follow-up
- one at 0.3mg/kg dose level no detectable antibody after dosing

No DLT observed

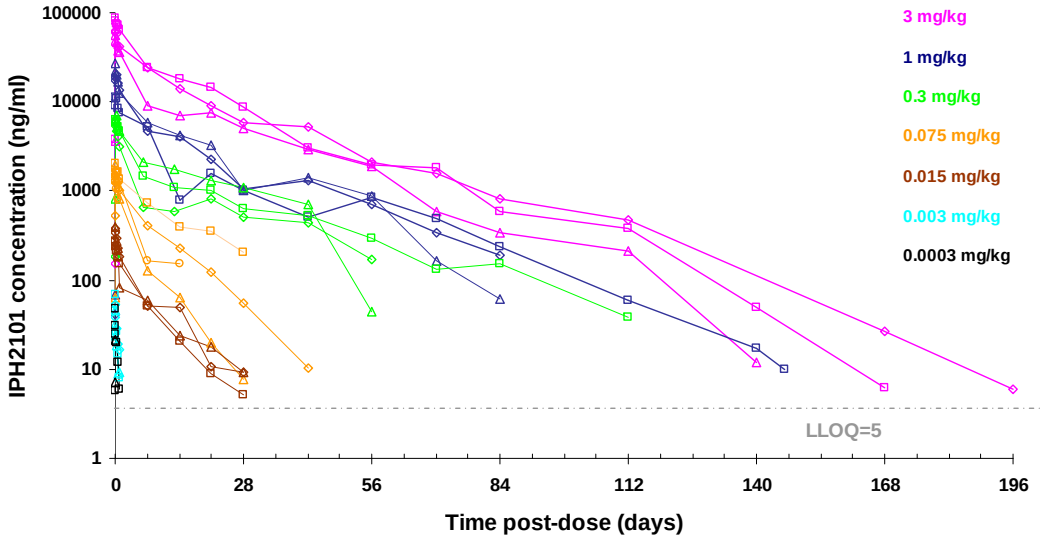
Related AEs graded by severity

CTCAE Preferred term	(total N=23 patients)		
	Grade 1	Grade 2	Grade 3
	N (%) E	N (%) E	N (%) E
Asthenia		1 (4%) 1	
Fever	2 (8%) 2	1 (4%)1	
Chills	1 (4%) 1		
Malaise/dizziness	1 (4%) 1	1 (4%) 1	
Rash / Erythema	4 (17%) 4	1 (4%) 1	
Pruritus	4 (17%) 4	1 (4%) 1	
Sinus bradycardia	1 (4%) 1	1 (4%) 1	
Diarrhea	1 (4%) 1		
Lipase increased			1 (4%) 1
Anemia	1 (4%) 1		
Thombocytopenia	1 (4%) 1		
Gynecomastia		1 (4%) 1	

Pharmacokinetics/ Pharmacodynamics

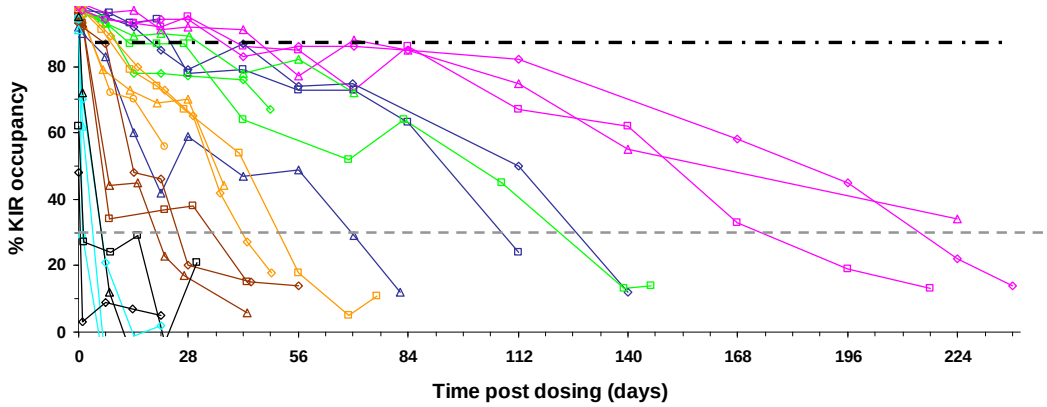
PK (serum concentration)

- Low inter-patient variability
- Half-life of IPH2101 is around 17 days



PD (KIR occupancy)

- Moderate inter-patient variability
- For doses above 1mg/kg, full saturation (>90% KIR occupancy) for 28 days.



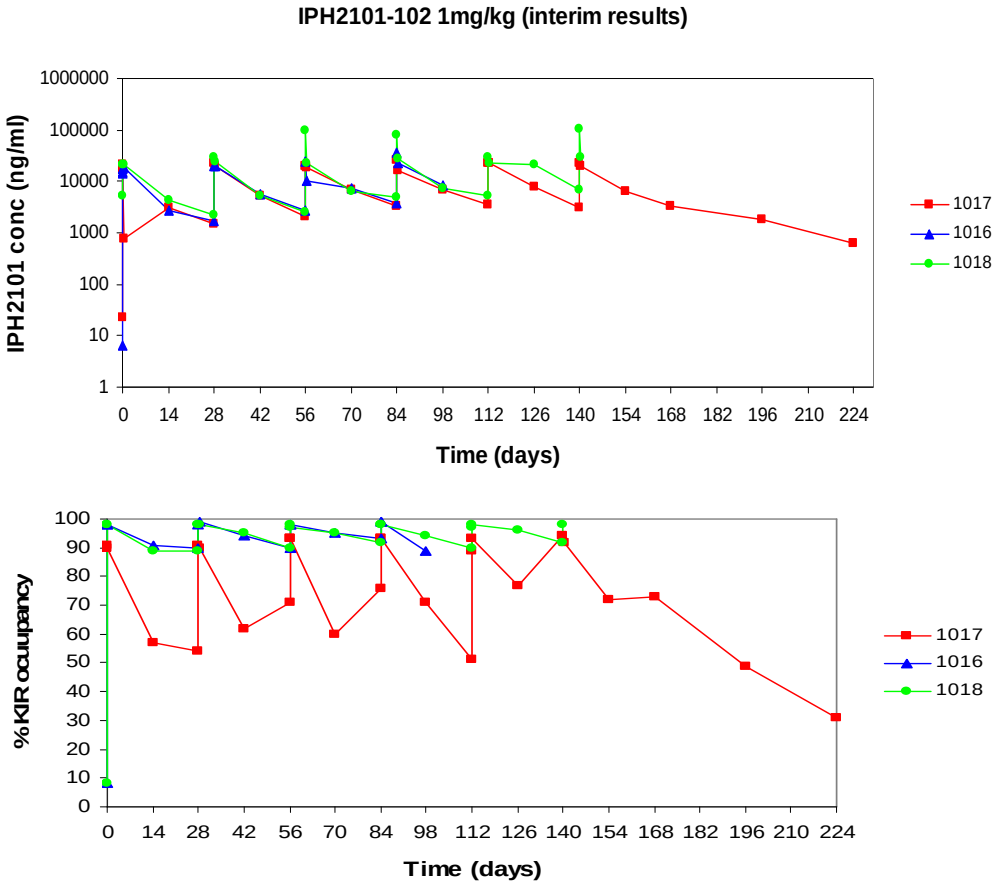
⇨ **Clear relationship between exposure (Cmax) and KIR-occupancy**

IPH2101 pharmacodynamics

- IPH2101 administration had no effect on
  - the number and distribution of the peripheral lymphocyte subsets
  - expression of inhibitory and activating NK receptors
    - NKR (KIRs, CD94/NKG2A, CD85j)
    - NCR (NKp46, NKp30) and NKG2D
- Not clinically relevant cytokine release
  - Modest and transient increase in serum IL-1b, IL-6, TNFa at highest doses
- No impairment of NK cell function tested by *ex vivo* cytotoxicity assay:
  - Chromium release assay
    - purified NK cells against K562
    - anti-CD16 and anti-NKp46 coated P815 cells
  - CD107 mobilization
    - purified NK cells against K562 , anti-CD16 and anti-NKp46 coated P815 cells

Repeated dosing (protocol IPH2101-102)

Dose Level	Dose (mg/kg)	No. of Patients	No. of cycles
1	0.0003	n=2	6 - 3
2	0.003	n=2	2 - 1
3	0.015	n=1	5
4	0.075	n=0	
5	0.3	n=0	
6	1	n=3	6 – 4 - 6
7	3	n=1	2 (ongoing)



Conclusions

- IPH2101 anti-KIR mAb shows a good safety profile with mild and transient AEs up to the maximal dose tested of 3 mg/kg
- A pharmacologically active dose has been identified
  - >90% KIR occupancy during 4 weeks, in the absence of DLT at 1 mg/kg
- Ongoing follow-up study
  - Repeated dosing with 1 mg/kg dose level
  - Assessment of
    - NK-cell functions following long term exposure
    - Clinical outcome