A Phase I study of the anti-Natural Killer (NK) Inhibitory Receptor (KIR) monoclonal antibody IPH 2101 in elderly patients with Acute Myeloid Leukemia (AML)

**IPH 2101 (1-7F9)**
- **Non-depleting full human IgG antibody**
- **Binds with high affinity to KIR2DL and KIR2DL3**
- **Blocks the interaction of KIRSL1 with HLA-C antigens, their natural ligands**
- **Prevents the inhibitory signals usually triggered by the KIRSL1/KIR2DL contact and thus blocks activation of NK cells**

**Clinical background and rationale**
- **AML is a disease of increasing incidence in the elderly**
- **Progressive CR of AML in the elderly is poor (survival of approximately 5% at 5 years)** due to chemotherapy resistance and comorbidity. Although CR rate ranges between 55-65%, most of the patient relapse shortly.
- **There is a need for non-cytotoxic therapeutic approaches. Maintenance strategies using immunotherapy might prolong remission duration and improve survival**

**Study design and endpoints**
- **Open label, single dose escalation and safety study**
- **Each patient allocated to one dose** (3 patients per dose group and 3 additional patients in case of DLT) and monitored for safety, pharmacokinetics and pharmacodynamics until no detectable KIR-occupancy on the patient-NK cells.
- **Dose escalation from 0.0003 to 3 mg/kg**
- **Dose escalation decision based on data obtained during the first 4 weeks post dosing**
- **Target occupancy: KIR full occupancy (<45%) for at least 4 weeks**

**PK/PD results**
- **Full blown pharmacodynamic relationship** between exposure (Cmax) and KIR-occupancy in accordance to the pre-clinical PK/PD model
- **Given KIR2DL occupancy above 60% (90% confidence level)**, full saturation has been observed for 28 days

**Overall Safety**
- **No DLT**
- **One SAE related: a patient (1019) died at 3.5 mg/kg experienced renal failure, hypertension (systolic >180 mmHg) and transaminase (platelets 55 grade 2) but considered as medically significant**
- **The patient underwent rapid (45 hrs) without specific treatment**
- **Related AE: drug administration were normal and transient with light infusion symptoms (fever, asthenia, headache) were mild**
- **IPH 2101 (1-7F9) up to 3 mg/kg showed a very good safety profile with mild and transient AEs medically manageable up to the maximal dose tested of 3 mg/kg**
- **Full KIR occupancy (>90%) during 4 weeks. In the absence of DLT, the maximal dose of 3 mg/kg was selected**

- **In the ongoing follow-up study we will collect information on prolonged exposure to IPH-2101, NK-cell functional studies, clinical outcome and pharmacoeconomics. Further clinical development of IPH 2101 as a therapy for various hematological malignancies, both as a single agent and in combination with other agents, is warranted and planned**