# Excellent non clinical safety profile of IPH4102, the first anti-KIR3DL2 mAb for the treatment of CTCL

Take me home !

Cécile Bonnafous[1], Anne Marie-Cardine[2], Ariane Thielens[1], Carine Paturel[1], Stéphanie Chanteux[1], Armand Bensussan[2], Martine Bagot[2] and Hélène Sicard[1]

[1]Innate Pharma, 117 Av de Luminy – 13009 Marseilles, France; [2]INSERM U976, Hôpital Saint Louis – 75475 Paris, France

## Abstract

IPH4102, the first-in-class anti-KIR3DL2 antibody, was granted Orphan Drug Designation in Europe for the treatment of Cutaneous T-Cell Lymphoma (CTCL), a rare disease with high unmet medical need.

IPH4102 has shown potent anti-tumor efficacy in *in vitro* and *in vivo* models (Marie-Cardine *et al*., Can. Res. 2014). In particular, IPH4102 mediates the killing of primary CTCL cells through ADCC by autologous, CTCL patient-derived NK.

To prepare the First-in-Human (FiH) clinical trial of IPH4102 in CTCL patients, we thoroughly addressed its safety profile in various non-clinical *in vitro* and *in vivo* systems. The immuno-pharmacology properties of IPH4102 were studied on human cells, in comparison with alemtuzumab, the potent yet highly immunosuppressive anti-CD52 antibody used as salvage therapy in advanced CTCL patients. The cynomolgus monkey was established as the sole phenotypically and functionally relevant animal species for IPH4102 toxicology studies, which comprised weekly IV administrations at different doses to support the intended therapeutic regimen.

*In vitro*, IPH4102 induces robust NK cell activation (through induction of CD137 and CD69) and mild cytokine production, although only in the presence of KIR3DL2-positive tumor cells. Interestingly, NK cells that normally express KIR3DL2 are poorly depleted by IPH4102, in sharp contrast with what is observed using alemtuzumab.

Furthermore, IPH4102 is well tolerated in cynomolgus monkeys, and weekly IV administrations of doses up to 100 mg/kg do not result in clinically meaningful, safety-related findings.

Taken together, these studies establish the highly favorable non clinical safety profile of IPH4102 and provide relevant markers to follow-up its immune-pharmacological effects that will be applied in the forthcoming Phase I trial.

## IPH4102 Non clinical safety risk assessment

### Part 1: KIR3DL2 target expression pattern

#### Flow cytometry

- ✓ KIR3DL2 expressed on ~34% NK cells, ~9% CD8$^+$ and ~3% CD4$^+$ T cells in blood (median values on n = 40 donors)
- ✓ KIR3DL2 not expressed on regulatory CD4$^+$ T cells
- ✓ KIR3DL2 expressed on ~25% of skin resident CD4$^+$ T cells (Sako, 2014)
- ✓ KIR3DL2 not expressed on CD34$^+$ progenitors

#### Immunohistochemistry

- ✓ KIR3DL2 not expressed on the 42 normal Human tissues of the FDA panel

### Part 2: Uncontrolled immune activation

#### Context

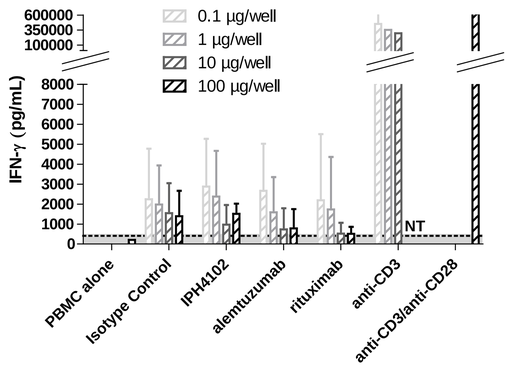
- ✓ Required post-TGN1412 test to evaluate safety risk of mAbs

#### Objective

- ✓ Assess risk of unintended/uncontrolled immune activation, i.e. induction of lymphocyte proliferation and/or massive cytokine release when cross-linked

#### Method

- ✓ n = 5 donors
- ✓ Measure release of different cytokines (MIP1β, TNFα, INFγ, MCP1, IL8 and IL6) and proliferation
- ✓ Compare to approved mAbs (rituximab, alemtuzumab) and true agonistic anti-CD3 and anti-CD28 mAbs

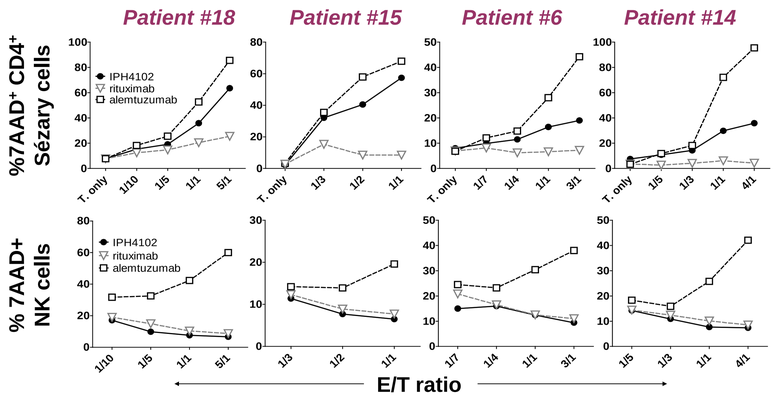



#### Results

- ✓ IPH4102 induces moderate cytokine release that is:
  - *much lower than agonistic mAbs*
  - *similar to alemtuzumab and rituximab*
  - *mainly driven by Fc binding rather than target binding*
- ✓ IPH4102 induces no lymphocyte proliferation in the chosen experimental conditions

## IPH4102 kills KIR3DL2$^+$ CTCL cells, but spares KIR3DL2$^+$ NK cells in an autologous ADCC assay

IPH4102 was evaluated in an autologous ADCC assay using NK cells and primary CTCL cells sorted from Sézary patient blood samples (n = 4 representative examples).
Increasing effector-to-target ratios (E/T) were performed according to numbers of recovered cells. 7AAD incorporation was used as surrogate marker of cell death. mAbs were incubated at 10 µg/mL, including positive control alemtuzumab and negative control rituximab, for 4 to 5 hours.




## IPH4102 toxicological evaluation in Non Human Primate (NHP)

### Species qualification: NHP *versus* Human comparison

- ✓ Phenotypically:
  - IPH4102 binding pattern to blood cells from both species
  - IHC staining on healthy tissues
- ✓ Functionally:
  - IPH4102 binding to Fc-Receptors in Surface Plasmon Resonance
  - Ability to activate and induce killing of KIR3DL2$^+$ tumors in PBMC from both species

### IND-supportive toxicology study design in NHP

- ✓ 0, 5, 50 and 100 mg/kg IV 4 times weekly
- ✓ 3+3 animals per dose
- ✓ 2 suppl. “recovery” groups (2+2 animals) at 0 and 100 mg/kg, left in observation for 6 more weeks before sacrifice
- ✓ Full clinical (morbidity/mortality, clinical signs, ECG, blood pressure, ophthalmology), blood biochemistry, hematology and anatomo-pathology (organ weight, macroscopic & microscopic changes) work up
- ✓ Toxicokinetics (TK) and Anti-Drug Antibody (ADA) assessments
- ✓ Plasma cytokines measured within 48h hours post injections #1 and #4
- ✓ Immuno-monitoring of blood cells (flow cytometry)
- ✓ Follow-up of KIR3D-expressing cells in quantitative RT-PCR (qRT-PCR)

### Key Results

- ✓ No clinically meaningful safety related findings in NHP, including in the anatomo-pathology part
- ✓ Dose-related exposure (PK characteristics in agreement with humanized IgG1)
- ✓ No ADA (whatever dose or time-point) so exposure to IPH4102 achieved as planned for each dose; no decrease in PK due to ADA
- ✓ Injection and dose-dependent decrease in KIR3D-expressing cells in blood as analyzed in qRT-PCR

## Calculation of IPH4102 First Human Dose with a MABEL strategy

*MABEL: Minimal Anticipated Biological Effect Level*

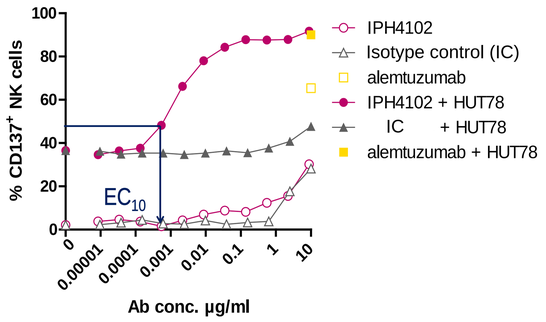
### Method

- ✓ PBMC from healthy donors (n = 15) spiked with HUT78 Sézary cell line or
- ✓ PBMC from Sézary patients (n = 5) (containing their own tumor cells)
- ✓ *In vitro* assay that recapitulates all features of IPH4102 Modes-of-Action:
  - Immune activation (= pharmacology/safety) -> CD137 induction on NK
  - Cytokine release (= pharmacology/safety) -> TNFα, IFNγ, MCP1, IL8…
  - Tumor lysis (= pharmacology/safety/efficacy) -> $^{51}$Cr release (for allogeneic assay only)

### Objective

- ✓ Establish a Minimal Anticipated Biological Effect Level *in vitro*
- ✓ Derive initial Human doses from *in vitro* concentrations achieving the MABEL

Representative data for 1 healthy donor, 1 read-out only (CD137 induction on NK cells) and principle for calculation of starting clinical dose:




$EC_{10}$ = X µg/mL ->
**based on animal PK modeling ≡ Y mg/kg IPH4102**

## Conclusions

In *ex vivo* autologous ADCC assays with Sézary patient cells, IPH4102 selectively kills primary KIR3DL2$^+$ tumors and spares NK effector cells. In an IND-supportive toxicology study in cynomolgus monkey, IPH4102 administration IV 4 times weekly, up to 100 mg/kg, did not result in clinically relevant safety related findings. IPH4102 does not present significant risk of uncontrolled immune activation in an *in vitro* solid phase assay in the presence of human PBMC. The starting dose of IPH4102 for the FIH Phase I trial is currently being calculated according to a MABEL strategy.

Based on its non clinical efficacy and safety profiles, IPH4102, the lead humanized anti-KIR3DL2 mAb is ready to be administered to advanced CTCL patients in a FIH Phase I clinical trial.