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

Cécile Bonnafous1, Anne Marie-Cardine2, Ariane Thielen1, Carine Paturel1, Stéphanie Chanteau1, Armand Bensussan2, Martine Bagot2 and Hélène Sicard1

1Innate Pharma, 117 Av de Luminy – 13009 Marseilles, France; 2INSERM 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 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 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

- **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, TNFa, 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

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

**MABEL: Minimal Anticipated Biological Effect Level**

- **Method**
  - PBMC from healthy donors (n = 15) seeded with HUT78 Sézary patient cell line
  - 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) → TNFa, IFNγ, MCP1, IL8...
    - Tumor lysis (= pharmacology/safety/efficacy) → 51Cr 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

**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 vivo 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.