KIR3DL2 is expressed irrespectively of disease stage in all subtypes of CTCL, with the highest prevalence in Sézary Syndrome (SS) and transformed Mycosis Fungoides (MF), two subsets with high unmet need. KIR3DL2 belongs to the killer immunoglobulin-like receptor (KIRs) family found on minor populations of NK and T cells. IPH4102 is a first-in-class anti-KIR3DL2 mAb. It selectively depletes KIR3DL2+ cells and has shown potent efficacy in preclinical models.

Secondary objectives include PK, immunogenicity and signals of anti-neoplastic clinical activity. Exploratory biomarkers aim to characterize and monitor KIR3DL2-expressing and non-expressing cells in involved organs along IPH4102 treatment. Exploratory assessments include SS pts’ NK cell function ex vivo. Study design and patient status are presented on poster O-03.

Study objectives

Primary objectives:
- To characterize the DLT and (S)AEs
- To monitor immune cell activation in blood
- To explore NK & macrophage infiltration in lesions
- To assess MRD (TCR-Vβ chain rearrangement)
- To assess cytokine release
- To assess NK cell function pre-dose

Secondary objectives:
- To explore antitumor activity
- To assess PK and immunogenicity

Translational objectives, biomarker exploration:
- To monitor KIR3DL2+ cells in skin, blood and LN
- To monitor immune cell activation in blood
- To explore NK cell function in involved organs along IPH4102 treatment

Exploratory assessments include SS pts’ NK cell function ex vivo. Study design and patient status are presented on poster O-03. Enrollment started in Nov 2015. Dose levels 1-7 have been completed without DLT, with 16 pts treated and evaluable for safety and clinical activity. They comprise SS, MF and 1 CD4+. NOS CTCL. Preliminary safety and clinical activity results from pts treated up to dose-level 7 are discussed in poster O-03. Preliminary results for PK and pharmacodynamics in skin and blood, are presented here.

PK in IPH4102-101 (NCT02590343) is a first-in-human phase I study evaluating IPH4102 in relapsed/refractory CTCL patients (pts). The primary objective is to assess the safety and tolerability of IPH4102 by characterizing DLT and AE. Secondary objectives include PK, immunogenicity and signals of anti-neoplastic clinical activity. Exploratory biomarkers aim to characterize and monitor KIR3DL2-expressing and non-expressing cells in involved organs along IPH4102 treatment. Exploratory assessments include SS pts’ NK cell function ex vivo. Study design and patient status are presented on poster O-03.

Abstract

KIR3DL2 is expressed irrespectively of disease stage in all subtypes of CTCL, with the highest prevalence in Sézary Syndrome (SS) and transformed Mycosis Fungoides (MF), two subsets with high unmet need. KIR3DL2 belongs to the killer immunoglobulin-like receptor (KIRs) family found on minor populations of NK and T cells. IPH4102 is a first-in-class anti-KIR3DL2 mAb. It selectively depletes KIR3DL2+ cells and has shown potent efficacy in preclinical models.

Secondary objectives include PK, immunogenicity and signals of anti-neoplastic clinical activity. Exploratory biomarkers aim to characterize and monitor KIR3DL2-expressing and non-expressing cells in involved organs along IPH4102 treatment. Exploratory assessments include SS pts’ NK cell function ex vivo. Study design and patient status are presented on poster O-03. Enrollment started in Nov 2015. Dose levels 1-7 have been completed without DLT, with 16 pts treated and evaluable for safety and clinical activity. They comprise SS, MF and 1 CD4+. NOS CTCL. Preliminary safety and clinical activity results from pts treated up to dose-level 7 are discussed in poster O-03. Preliminary results for PK and pharmacodynamics in skin and blood, are presented here.

Conclusions on preliminary results of biomarkers

- Preliminary results (up to 1.5 mg/kg) show IPH4102 PK is linear. Cmax increases in a dose-dependent fashion and there is no unexpected accumulation following QW administrations.
- In blood, irrespective of circulating tumor burden, 0.75 mg/kg QW seems to fully saturate KIR3DL2 on tumor cells.
- Clinical responses in blood are in agreement with centrally-performed immuno-monitoring results.
- Changes in KIR3DL2 staining in skin lesions tend to be associated with changes in weighted mSWAT and objective clinical response in skin.
- Follow-up of CD4+ T cells in skin lesions tends to confirm that tumor cells are actually depleted and normal immune system restored in lesions (decrease in skin-resident CD4+CD8+).
- So far, for all SS patients tested, ex vivo ADCC assay shows potent NK function pre-dose against autologous blood tumor cells.
- Three more dose-levels remain to be evaluated to confirm these preliminary findings (3, 6 and 10 mg/kg).

Case Study

**Patient 01-013**: 74-year old male with SS diagnosed in MAR 2013. Eight times of previous therapies (incl. ECP + bexarotene + INFα, methotrexate, mohsurgery, ECP + INFα + methotrexate, nim看出lin, bex. + INFα, TNFα, at study entry. Started at 0.05 mg/kg IPH4102 on 2JAN16.**

- *Medium* blood tumor and KIR3DL2 burdens: *1,300 KIR3DL2 CD4+ cell – 4,600 aberrant cells/µL blood (86% among lymphomas).

- Skin lesions showed decreased CD4+ staining and parallel increase in CD8 T cells over time.

- Both parameters confirm the actual depletion of skin-resident tumor cells and potential restoration of a normal immune system in skin lesions.

Individual patients’ correlative results

- Regular decrease in blood tumor cells (CD4/CD8/CD4+ T cells) and KIR3DL2+ CD4+ T cells starting immediately after the 1st administration.
- PR in blood observed at W5 and CR at W10 (ongoing) (based on local assessment).
- Full occupancy of KIR3DL2 on tumor CD4+ T cells.
- "Long lasting" (>67 days, ongoing) global clinical PR and progressive decrease in mSWAT are consistent with almost complete loss of KIR3DL2 staining in HC.

- Skin lesions decreased CD4+ staining and parallel increase in CD8 T cells over time.
- Both parameters confirm the actual depletion of skin-resident tumor cells and potential restoration of a normal immune system in skin lesions.

- Delayed onset of blood PR (local assessment), achieved at W14 (ongoing), matching decrease in blood tumor cell counts.
- Full occupancy of KIR3DL2 on CD4+ T cells achieved rapidly and sustained.

- NK cells from Sézary patient 01-013 mediate potent ADCC with IPH4102 against primary autologous tumor cells (same legend as above).