First-in-human, open label, multicenter Phase I of IPH4102,
first-in-class humanized anti-KIR3DL2 mAb, in relapsed/refractory cutaneous T-cell lymphomas

Abstract (TPS2591)

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Background

Cutaneous T-cell lymphomas (CTCL) comprise a heterogeneous group of T-cell derived malignancies that arise primarily in skin. There is no standard of care in CTCL, and current treatment options have limited efficacy in advanced disease.

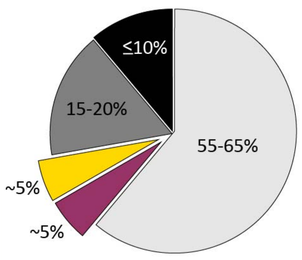
KIR3DL2 is consistently expressed in all subtypes of CTCL, irrespectively of disease clinical stage, with the greatest expression in Sézary Syndrome (SS) and transformed Mycosis Fungoides (MF), two subsets with high unmet need. KIR3DL2 belongs to the killer immunoglobulin (Ig)-like receptor (KIRs) family and is also expressed on minor populations of normal NK, CD8 and CD4 T cells.

IPH4102 is a first-in-class anti-KIR3DL2 monoclonal antibody (mAb). It depletes KIR3DL2-expressing tumor cells. Its modes of action include Antibody-Dependent Cell-Cytoxicity (ADCC) and –Phagocytosis (ADCP). IPH4102 has potent efficacy in non-clinical models, in particular *ex vivo* autologous assays using primary CTCL cells (Marie-Cardine *et al*, Cancer Res. 2014).

IPH4102-101 (NCT02593045) is a first-in-Human Phase I study of single-agent IPH4102 in relapsed / refractory CTCL.

CTCL Landscape

Frequency of CTCL subtype per WHO-EORTC classification and respective 5-year survival rates



KIR3DL2 expression per CTCL subtype

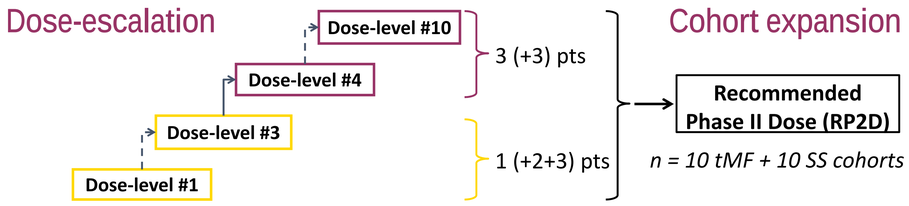
	5-year Overall Survival	%KIR3DL2⁺ skin biopsies (n=107 CTCL patients)
Mycosis Fungoides (MF)	95 to 20%*	~45%
Transformed MF	≤ 15%	> 80%
CD30⁺LPD (ALCL)	75 to 96%*	100%
Sézary Syndrome	~10%	> 85%
Others (ATL, NK/T, γδ, ...)	≤ 20%	~35% to 100%

**depending on TNMB stage*

Study Design

The study has two sequential portions, a dose-escalation followed by cohort expansion. IPH4102 first Human dose was selected based on a MABEL strategy (from an *in vitro* assay of cytotoxic activity) and subsequent dose-levels were chosen through PK/PD modeling using animal exposure and efficacy data.
In the dose-escalation portion, a 3+3 design with accelerated titration is employed.

The dose that will be used in the cohorts (RP2D) will be selected based on the results from the dose-escalation portion. Cohort design (numbers, CTCL subtypes…) may be revisited according to dose-escalation findings.



Patient Population

Key Inclusion Criteria

- Pts with relapsed/refractory primary CTCL who have received at least 2 previous systemic therapies and if MF/SS have stage IB - IVB at study entry.
- Centrally assessed KIR3DL2 expression on malignant cells in blood or in at least 1 skin lesion.
- Pts must have the following min. wash-out periods:
  - ≥12 weeks for TSEB irradiation,
  - ≥4 weeks for mAbs (≥ 8 for alemtuzumab),
  - ≥ 3 weeks for local radiation therapy, syst. cytotoxic anticancer therapy, treatment with other anti-neoplastic agents
  - ≥3 weeks for syst. retinoids, IFNs, vorinostat, romidepsin, fusion proteins
  - ≥3 weeks for phototherapy
  - ≥2 weeks for topical therapy
- Adequate baseline laboratory values
  - hematology: hemoglobin >9 g/dL, ANC ≥1,000/µL, CD4≥200/µL, platelets ≥50,000/µL,
  - biochemistry: bilirubin ≤1.5 X ULN or ≤3 X ULN for patients with Gilbert's disease, serum creatinine ≤1.5 X ULN, ALT or AST ≤3X ULN.

Key Exclusion Criteria

- Limited disease (if MF/SS: stage IA) or CNS disease.
- Clinical relevant AEs or laboratory results related to previous anti-neoplastic therapy that have not resolved to a NCI-CTCAE grade ≤1.
- Concomitant corticosteroid use, systemic or topical (WHO class I & II), for skin disease.
- Pts who have undergone a stem cell transplantation.
- Pts with known NCI CTCAE Grade 3 or higher (requiring IV antibiotics) active systemic or cutaneous viral, bacterial, or fungal infection.
- Prior hypersensitivity reaction to monoclonal antibodies, other therapeutic proteins, or immunotherapy.

Enrolment status

Enrolment into study IPH4102-101 started in November 2015 and is currently ongoing.

Study Objectives

Primary Objective

- To assess the safety and tolerability of increasing IV doses of single agent IPH4102 by characterizing the dose limiting toxicities (DLT) and (S)AEs
- To identify the MTD or determine a dose for further studies (RP2D)

Secondary Objectives

- To explore antitumor activity
- To assess pharmacokinetics (PK)
- To assess immunogenicity
- To explore pruritus

Exploratory Objectives

- To assess plasma cytokine released post administration
- To explore KIR3DL2-expressing cell changes in the peripheral blood (flow cytometry), skin lesions (IHC) and lymph nodes (IHC)
- To monitor other changes (phenotype & number) of circulating immune cells (flow cytometry)
- To explore NK cell and macrophage infiltration in skin lesions
- To assess expression of other immune receptors in skin lesions
- To assess Minimal Residual Disease (MRD)
- To explore blood NK cell function *ex vivo* pre-dose

Bibliography

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