BIOMARKERS OF PHARMACOLOGICAL AND CLINICAL ACTIVITY OF IPH4102, FIRST-IN-CLASS HUMANIZED ANTI-KIR3DL2 MAB, IN A PHASE I STUDY IN PATIENTS WITH RELAPSED/REFRACTORY CTCL

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KIR3DL2 IS A THERAPEUTIC TARGET IN CTCL

- KIR3DL2 belongs to the Killer Ig-like Receptor family of receptors that modulate NK and T cell activity
- KIR3DL2 is expressed on ~30% of normal NK and <10% normal T cells
- KIR3DL2 is expressed on CTCL cells (skin lesions and blood aberrant cells)
  > Irrespective of disease clinical stage
  > With a higher prevalence in Sézary syndrome (SS), CD30+ LPD and Mycosis fungoides with large-cell transformation
- KIR3DL2 may have prognostic significance in SS
- IPH4102 is an anti-KIR3DL2 IgG1 antibody that was selected and designed to specifically target KIR3DL2 and deplete KIR3DL2+ cancer cells

**IPH4102-101 PHASE 1 STUDY DESIGN AND OBJECTIVES**

- **Dose-escalation** (10 dose levels – accelerated 3+3 design) followed by cohort expansion
- **Primary objective**: determination of MTD and RP2D, overall safety
- **Secondary objectives**: clinical activity, PK/immunogenicity
- **Exploratory objectives**: changes in KIR3DL2+ cells in involved compartments, NK cell function pre-dose
- **Key inclusion criteria**:
  - Any CTCL subtype, ≥ 2 prior lines of systemic therapy, if MF/SS stage ≥ IB
  - > 5% aberrant cells KIR3DL2pos in skin or blood
  - Treatment until progression or unacceptable toxicity
- **Intra-patient dose-escalation allowed after W5**

**Diagram:**
- Dose-escalation (doses in mg/kg, n patients/dose)
- Cohort expansion in subtypes of CTCL
- RP2D for cohorts

**Table:**

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<th>Cohort</th>
<th>Dose (mg/kg)</th>
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<td>3</td>
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**Schedules:**
- 4 admin. weekly
- W5
- 10 admin. Q2W
- W26
- N admin. Q4W
METHODS FOR BIOMARKER ANALYSIS

• Immuno-monitoring in blood by flow cytometry:
  > Proportion of KIR3DL2 receptor occupancy by IPH4102
  > Absolute counts of aberrant cells (CD26⁻ and/or CD7⁻ CD4 T cells), clonal CD4 T cells (defined by their Vβ chain), KIR3DL2⁺ CD4 T cells
  > KIR3DL2⁺ “normal” lymphocytes (NK, CD8 T cells)

• Ex vivo function of NK cells at baseline in autologous ADCC assay (SS patients)

• Immuno-histochemistry (IHC) staining of KIR3DL2-expressing cells and other immune cell subsets (CD4, CD8,…) in skin biopsies
KIR3DL2 IS 100% OCCUPIED BY IPH4102 AT DOSES ≥ 0.75 MG/KG

KIR3DL2 occupancy on blood CD4+ T cells
1 week after the 1st administration of IPH4102

Available anti-KIR3DL2 clones:
• 2B12, same as IPH4102
• 13E4, binding to a different epitope than 2B12, to determine the “100% level”

Only applicable to SS patients with > 5% of KIR3DL2 on CD4+ T cells
BLOOD ABERRANT, CLONAL AND KIR3DL2⁺ CD4⁺ T CELLS ARE DEPLETED DURING IPH4102 TREATMENT

**Aberrant cells**

**Clonal cells**

**KIR3DL2⁺ CD4⁺ T cells**

Starting dose color code:
- 0.0001 mg/kg
- 0.001 mg/kg
- 0.05 mg/kg
- 0.2 mg/kg
- 0.75 mg/kg
- 1.5 mg/kg
- 3 mg/kg
- 6 mg/kg
- 10 mg/kg

Wee k s a f te r t he 1 st a d m i n i s t r a t i o n
N b e r o f V B + C D 4 + c e l l s / µ L

Wee k s a f te r t he 1 st a d m i n i s t r a t i o n
N b e r o f K I R 3 D L 2 + C D 4 + T c e l l s / µ L

(n = 20 SS)
(n = 11 SS)
(n = 20 SS)
ABERRANT BLOOD CELLS CHANGES FROM BASELINE TEND TO BE RELATED TO GLOBAL CLINICAL RESPONSE

KIR3DL2+ CD4+ T cells

versus best Global Response

Aberrant CD7- and/or CD26- CD4+ T cells

versus best Global Response

Best global response: CR PR SD PD (n = 20 SS)
SS PATIENT NK CELLS ARE FUNCTIONAL EX VIVO AT BASELINE AND NOT DEPLETED IN BLOOD DURING TREATMENT

Blood NK cells absolute counts

(n = 20 SS)
PERCENTAGE OF KIR3DL2+ CELLS CHANGES FROM BASELINE IN SKIN BIOPSIES TEND TO BE RELATED TO CLINICAL RESPONSE

Relation to response in skin at W14

Relation to best Global Response

SCR: 52% KIR3DL2+ cells

Week 14: 0.2%

1 plot / biopsy, 1 or 2 biopsies / patient – n = 22 patients - percentage of KIR3DL2+ cells among mononuclear cells
HIGHER CD8\(^+\) CELLS AT SCREENING IN LESIONS TEND TO BE RELATED TO GLOBAL CLINICAL RESPONSE

Best global response: CR, PR, SD, PD

1 plot / biopsy, 1 or 2 biopsies / patient – n = 22 patients - percentage of CD4 or CD8\(^+\) cells among mononuclear cells
PATIENTS WITH CR/PR SHOW AN INCREASE OF %CD8\(^+\) IN THE SKIN

**Variation of %CD8\(^+\) cells in skin biopsies during treatment versus best Global Response**

15% of mononuclear cells: 560 cells/mm\(^2\)

30% of mononuclear cells: 805 cells/mm\(^2\)

30% of mononuclear cells: 713 cells/mm\(^2\)

Best global response: CR, PR, SD, PD
ANALYSIS OF CD163⁺ CELL CHANGES IN THE TUMOR MICROENVIRONMENT DURING IPH4102 TREATMENT

%CD163⁺ within 30 µm of CD4⁺ cells in skin biopsies versus best Global Response

CD163⁺ average distance (µm) to CD4⁺ cells in skin biopsies versus best Global Response

HALO software analysis
CONCLUSIONS AND PERSPECTIVES

• IPH4102 was evaluated in a dose-ranging first-in-man Phase 1 trial in relapsed advanced CTCL patients and was found safe and clinically active across all doses tested (see Bagot et al abstract O-53)
• KIR3DL2 full occupancy on blood CD4 T cells by IPH4102 is achieved at doses ≥ 0.75 mg/kg
• Sézary patient NK cells are functional pre-dose and are not decreased during treatment
• IPH4102 is pharmacologically active at all dose-levels tested:
  > KIR3DL2+ cells are depleted in blood, similarly to aberrant and clonal CD4 T cells
  > KIR3DL2+ cells are depleted in skin lesions
• Some biomarkers in blood and skin tend to be associated with global clinical response
  > Decrease in KIR3DL2+ cells in blood and skin during treatment
  > Higher CD8+ cells in lesions at baseline and increase during treatment
• These results deserve to be confirmed in the cohort-expansion part of the study, where additional patients will be treated at the RP2D
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All our patients and their families...