**Abstract**

KIR3DL2 is expressed in all subtypes of CTCL, irrespective of clinical stage, with the highest prevalence in Sézary syndrome. KIR3DL2 is well tolerated in an heavily pretreated patient population: no DLTs were reported. The last two dose-levels remain to be evaluated.

**Study design**

- **Primary objectives:** To assess safety & tolerability of repeated administrations of IPH4102 by:
  - Characterizing the DLT (and SAEs) (based on the mSWAT score)
  - To assess PK and tolerability
- **Secondary objectives:**
  - To explore antitumor activity
  - To assess PK and pharmacodynamics
- **Translational objectives, biomarker exploration:**
  - To monitor KIR3DL2+ cells in skin, blood and urine
  - To explore immune activation in blood
  - To assess NK and macrophage infiltration in skin lesions
  - To assess MRP (Monocytic/Respiratory Natural Killer Cells) in skin
  - To assess NK cell function pre-dose

**Key eligibility criteria**

- Patients with refractory cutaneous T-cell lymphoma who have received ≥ 2 prior systemic therapies
- For MD Anderson Cancer Center patients, clinical stage ≥ II

**Baseline characteristics**

| Subtype | Patients (n) | Stage of disease | Sex | Age (median) | Race | Prior systemic therapies | ECOG performance status
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<td>IA-IX</td>
<td>10</td>
<td>70.0</td>
<td>2</td>
<td>6/10/4</td>
<td>1</td>
</tr>
<tr>
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<td>IA-IX</td>
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<td>75.0</td>
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**Immuno-monitoring of blood cells**

- Increase in blood tumor cells (CD8+ T cell) and KIR3DL2+ CD4+ T cells starting immediately after the 1st administration
- NK cell assay: No NK cell activity was observed for this cohort (based on local assessment)
- Full occupancy of KIR3DL2 on CD4+ T cells achieved rapidly

**Ex vivo ADCC assay**

- Autoimmune NK-mediated death of KIR3DL2+ CD4+ T cells induced by IPH4102

**MRD in skin (biopsy) & blood**

- 2 dominant clones found pre-dose in skin and blood
- Both substantially decreased by wk 10 in skin, biopsy and blood (still above detection limit)

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**Preclinical safety results**

- All 13 pts are evaluable for safety and efficacy, including 13 SS, 2 MF and 1 CD4+ TCL NOS
- ECOG performance status 1-2 previous systemic therapies
- Centrally-assessed KIR3DL2 expression

- No AE led to treatment discontinuation
- 1 death reported for severe neutropenia (AE of sepsis)
- Rare/Serious AEs: all asymptomatic, T cell flare (1), mono/lymphocytosis (1), all tested patients had a previous history of hematological disease

**Individual patient’s correlative results**

**Patient #10-005: 77-year old female with SS diagnosed in NOV 2008. Six lines of previous therapies (including ECP + bexarotene + IFN + methotrexate, romidepsin, romidepsin, + [INF]x2, TCVR-2, Biopterin and CTCL NOS).**

- Disease) clonal TCR-V β rearrangement
- For this study, the biopsies were taken at baseline (wk 0)
- The last two dose-levels remain to be evaluated

- Changes in weighted mSWAT and objective clinical response in skin and blood tend to be associated with changes in KIR3DL2 staining, as well as changes in MRD
- Responders show decrease in CD4/CD8 ratio in skin and in blood
- So far, for all 3 pts tested, ex vivo ADCC assay shows potent NK function pre-dose against autologous blood tumor cells
- Dose-level 3-5 mg has been completed without DLT occurrence

**Study objectives**

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