PHASE I OF IPH4102, ANTI-KIR3DL2 MAB, IN RELAPSED/REFRACTORY CUTANEOUS T-CELL LYMPHOMAS (CTCL): DOSE-ESCALATION SAFETY, BIOMARKER AND CLINICAL ACTIVITY RESULTS

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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, FIRST-IN-CLASS ANTI-KIR3DL2 MAB ATTRIBUTES

- IPH4102 is a humanized antibody that targets and selectively depletes KIR3DL2-positive cells
- Its modes-of-action include ADCC and ADCP (Ab-dependent cell cytotoxicity and phagocytosis)
- IPH4102 has shown potent pre-clinical efficacy:
  > In mouse models of KIR3DL2-positive tumor cells
  > In *ex vivo* autologous assays using patient-derived NK and Sézary cells

**Mice engrafted iv with KIR3DL2⁺ tumors**

**% of 7AAD⁺ (ie dead) Sézary cells**

Marie-Cardine *et al*, 2014, Cancer Res. 74(21)
• 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, Molecular Residual Disease (MRD), NK cell function pre-dose
• **Key inclusion criteria:**
  - Any CTCL subtype, ≥ 2 prior lines of systemic therapy, if MF/SS stage ≥ IB
  - > 5% aberrant lymphocytes express KIR3DL2 in ≥ 1 skin lesion or in blood
• Treatment until progression or unacceptable toxicity
• Intra-patient dose-escalation allowed after W5
BASELINE DISEASE CHARACTERISTICS (AS OFF MAY 10, 2017)

<table>
<thead>
<tr>
<th>Age (years), median (min; max)</th>
<th>All doses N = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> (years), <strong>median</strong> (min; max)</td>
<td>71 (42; 90)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MF/SS CTCL type, n (%)</th>
<th>Mycosis fungoides (MF)</th>
<th>Sézary Syndrome (SS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (16)</td>
<td>20 (80)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non MF/SS CTCL type, n (%)</th>
<th>CD4⁺ T-cell lymphoma, NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (4)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical stage (MF/SS), n (%)</th>
<th>IB</th>
<th>IIB</th>
<th>IVA1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (4.1)</td>
<td>3 (12.5)</td>
<td>20 (80)</td>
<td></td>
</tr>
</tbody>
</table>

| No. of regimen (systemic) received, median (min; max) | 4 (2; 10) |

- 25 patients treated: 25 evaluable for safety, 24 for clinical activity (1st clinical assessment of the last patient enrolled at 10 mg/kg occurred after data cut-off)
- Seven of screen failures (out of 9/34 pts screened) were due to lack of KIR3DL2 expression
- No dose-cohort had to be expanded for safety reasons
ADVERSE EVENTS POSSIBLY RELATED TO STUDY DRUG (> 5%; > 1 PATIENT)

- No DLT, MTD not reached

<table>
<thead>
<tr>
<th>Any related AE</th>
<th>Related AE (N = 25)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades n (%)</td>
<td>Grade 3 n (%)</td>
</tr>
<tr>
<td>Any related AE</td>
<td>13 (52)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>4 (16)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>3 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Hot flush</td>
<td>2 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>2 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>2 (8)</td>
<td>0</td>
</tr>
</tbody>
</table>

- No grade 4 or 5 related AEs
- Only 1 related SAE: grade 2 atrial flutter on the day of IPH4102 administration that did not reoccur at subsequent administrations
- One patient developed ADA -> recurrent IRR despite premedication
- N = 10 pts experienced infections, including n = 2 sepsis (including 1 death – S. aureus) but all deemed related to underlying disease and not to study drug
## PRELIMINARY CLINICAL RESPONSE RESULTS
(CUT-OFF DATE MAY 10, 2017)

<table>
<thead>
<tr>
<th>Best Response (n)</th>
<th>Best Response in all patients</th>
<th>Best Response in Sézary Syndrome patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Global N=24</td>
<td>Global n=19</td>
</tr>
<tr>
<td>CR</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PR</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>SD</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>PD</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td><strong>41.7 %</strong></td>
<td><strong>47.4 %</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DOR (days) - median</th>
<th>Not reached</th>
</tr>
</thead>
<tbody>
<tr>
<td>(min – max)</td>
<td>(64+ – 379+)</td>
</tr>
<tr>
<td>251</td>
<td>Not reached</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PFS (days) - median</th>
<th>329</th>
</tr>
</thead>
<tbody>
<tr>
<td>(min – max)</td>
<td>(28+ – 526+)</td>
</tr>
<tr>
<td>274</td>
<td></td>
</tr>
</tbody>
</table>

ORR: Overall Response Rate  
PFS: Progression-Free Survival  
DOR: Duration of Response

- Median follow-up time is 338 days
- Preliminary results are calculated for 24 patients (19 SS) evaluable for efficacy assessment, treated with doses ranging from 0.0001 to 10 mg/kg
- All clinical responses are confirmed
- 2 patients who were in global PR reached “near CR” skin response, ie >90% reduction in mSWAT
- Pruritus is notably decreased in patients with clinical response
TIME-COURSE OF GLOBAL RESPONSE FOR 24 EVALUABLE PATIENTS

Response evaluation according to International Consensus criteria (Olsen et al, JCO 2011)
Patient 11-005:
- 77-year old female
- **Sézary Syndrome** diagnosed in NOV 2008
- **6 lines of previous therapies** (incl. ECP + BEX + INFα, MTX, mogamulizumab, BEX, pembrolizumab)
  - Started at 0.05 mg/kg on 25JAN16
  - Global PR since W10 (0.05 mg/kg)

Patient 11-024:
- 75-year old male
- **Sézary Syndrome** diagnosed in AUG 2011
- **6 lines of previous therapies** (incl. MTX, INFα, vorinostat then mogamulizumab, BEX, pembrolizumab)
  - Started at 3 mg/kg on 16OCT16
  - Global PR since W14 (3 mg/kg)
**EXPLORATORY/PHARMACODYNAMICS ENDPOINTS**

**SKIN & BLOOD ASSESSMENTS / PT 11-005**

<table>
<thead>
<tr>
<th>SCRx</th>
<th>CD4/8 ratio in skin</th>
<th>mSWAT</th>
<th>% of KIR3DL2+ cells in skin lesions by IHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCR</td>
<td>52%</td>
<td>SCR: 49</td>
<td>SCR: 80.5/1/0</td>
</tr>
<tr>
<td>W5</td>
<td>4.4%</td>
<td>W5: 87/0/0</td>
<td></td>
</tr>
<tr>
<td>W10</td>
<td>36.5/0/0</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>W14</td>
<td>0.2%</td>
<td>W14: 19.3/0/0</td>
<td></td>
</tr>
</tbody>
</table>

**CD4/8 ratio in skin**

- SCR: 52%
- W5: 4.4%
- W10: 36.5/0/0
- W14: 0.2%

**mSWAT**

- SCR: 49
- SCR: 80.5/1/0

**% of KIR3DL2+ cells in skin lesions by IHC**

- SCR: 52%
- W5: 4.4%
- W10: 36.5/0/0
- W14: 0.2%

**MRD in skin**

- TCRVb07-03
- TCRVb20-01

**MRD in blood**

- TCRVb07-03
- TCRVb20-01

**Graphs:**

- KIR3DL2+ CD4+ T cell death
- CD4/8 ratio in skin
- MRD in skin
- MRD in blood

**Notes:**

- SCR = screening
- CR in blood since W10
- Vbeta-pos CD4 T (central)
- KIR3DL2-pos CD4 T (central)
- CD26-neg CD4 T (local)
IPH4102-101 HIGHLIGHTS
SAFETY, CLINICAL ACTIVITY AND BIOMARKERS

• IPH4102 MTD was not reached: well tolerated in an elderly and heavily pretreated (med. 4 prior lines) patient population
  > AE are typical for CTCL or reflects low grade infusion-related reactions
  > Only one related AE of grade 3 or higher occurred (at 0.2 mg/kg)
• Preliminary best global ORR is 41.7% in the evaluable population and 47.4% in SS patients
  > One global complete response was observed
  > 2 complete responses in skin and 5 complete responses in blood
  > Pruritus is substantially improved
• PK is typical for an IgG1 antibody; only 1 patient developed ADA
• Pharmacodynamic endpoints (monitoring of KIR3DL2-positive cells and MRD) are consistent with clinical activity results, confirming drastic elimination of neoplastic cells in skin and in blood, and potential restoration of skin normal immune system
• Patient NK cells pre-dose present robust ADCC activity ex vivo
• Expansion cohorts are planned to start in Q3 2017 at the RP2D, with 30 additional patients, including 15 more SS to confirm preliminary results
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All our patients and their families…