IPH4102, an anti-KIR3DL2 monoclonal antibody in refractory Sézary Syndrome: Results from a multicenter international phase 1 trial

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Advisory committee: Innate Pharma, Actelion, Takeda, Kyowa Kirin

Equity Ownership: Innate Pharma
IPH4102
FIRST IN CLASS mAb DIRECTED AGAINST KIR3DL2

NK cells kill primary Sézary cells in ex vivo autologous model through IPH4102-mediated ADCC

Marie-Cardine A et al, Cancer Res 2014
IPH4102 IMPROVES SURVIVAL IN MOUSE XENOGRAFT MODELS

Marie-Cardine A et al, Cancer Res 2014

Bagot M et al, ASH 2018
KIR3DL2 is expressed in CTCL particularly in Sézary Syndrome

Battistella M et al; Blood 2017

KIR3DL2 expression by IHC in a SS patient


Bagot M et al, ASH 2018
STUDY DESIGN
FIRST IN HUMAN PHASE 1 CLINICAL TRIAL

Dose-escalation

- 10 dose levels (up to 10mg/kg) – accelerated 3+3 design
- All CTCL subtypes
- ≥ 2 prior systemic therapies
- KIR3DL2 ≥5% in skin and/or blood (centrally)

Cohort expansion

- Recommended Phase 2 dose (750 mg)
- SS and tMF only
- ≥ 2 prior systemic therapies
- Any KIR3DL2 expression level

- **Dosing regimen**, until progression or unacceptable toxicity

- Intra-patient dose-escalation allowed after Week 5 (W5) in the dose-escalation portion

Bagot M et al, ASH 2018
STUDY OBJECTIVES

- **Primary objective**: determination of Maximal Tolerated Dose (MTD) and RP2D, overall safety

- **Secondary objectives**:
  - Overall Response Rate (ORR, Olsen JCO 2011 criteria), duration of response (DOR) and Progression-Free Survival (PFS)
  - PK and immunogenicity

- **Quality of Life**
  - Pruritus (Visual Analogue Scale)
  - SkinDex29

- **Exploratory objectives**:
  - Early changes (at week 5) in KIR3DL2-positive cells* and molecular residual disease (MRD)** in skin and blood and ORR

* By Immunohistochemistry (IHC); ** By TCR deep sequencing

TODAY’S PRESENTATION FOCUSES ON SS PATIENTS
# BASELINE DISEASE CHARACTERISTICS

## SÉZARY SYNDROME (N=35)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total N = 35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in years (range)</td>
<td>70 (37 – 90)</td>
</tr>
<tr>
<td>Evidence of LCT*, n (%)</td>
<td>7 (20%)</td>
</tr>
<tr>
<td>KIR3DL2 expression, n (%)</td>
<td></td>
</tr>
<tr>
<td>- Skin</td>
<td>27 (77%)</td>
</tr>
<tr>
<td>- Blood</td>
<td>33 (94%)</td>
</tr>
<tr>
<td>- Skin and/or blood</td>
<td>33 (94%)</td>
</tr>
<tr>
<td>Median time from diagnosis in months (range)</td>
<td>23 (6 – 268)</td>
</tr>
<tr>
<td>Median N. of prior systemic therapy (range)</td>
<td>2 (1 – 9)^</td>
</tr>
<tr>
<td>- Treated with IPH4102 as ≥ 5th line of systemic treatment</td>
<td>12 (35%)</td>
</tr>
<tr>
<td>Prior treatment with HDAC inhibitors, n (%)</td>
<td>13 (37%)</td>
</tr>
<tr>
<td>Prior treatment with Mogamulizumab, n (%)</td>
<td>7 (20%)</td>
</tr>
</tbody>
</table>

* LCT: large cell transformation based on central testing on frozen tissue.
^ One patient had a protocol violation, treated with only one prior line of systemic therapy

Bagot M et al, ASH 2018
SAFETY PROFILE
IPH4102 DISPLAYS A FAVORABLE SAFETY PROFILE

Dose escalation: no DLT / MTD not reached / RP2D = 10mg/kg - 750 mg flat dose

<table>
<thead>
<tr>
<th>Common AEs</th>
<th>All AEs</th>
<th>Related AEs*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>10 (29%)</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>9 (26%)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (23%)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>7 (20%)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7 (20%)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>6 (17%)</td>
<td>0</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>5 (14%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (14%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Only 3 patients (9%) stopped treatment for an AE
Four patients developed 5 possibly related grade ≥ 3 AEs
• grade 5 hepatitis (n=1)**, grade 4 sepsis (n=1), grade 3 lymphopenia (n=3), grade 3 hypotension (n=1).

Data Cut-off: October 15, 2018

* According to investigator assessment
** 6 weeks after stopping IPH4102, evidence of HHV-6B infection
CLINICAL EFFICACY RESULTS
HIGH OVERALL RESPONSE RATE

Best global response
42.9% (95% CI: 28.0 – 59.1)

Data Cut-off: October 15, 2018
CLINICAL EFFICACY RESULTS

DURABLE RESPONSES

Duration of response, median (95% CI)
13.8 months (7.2 – NR)

Data Cut-off: October 15, 2018

NR: Not Reached
**CLINICAL EFFICACY RESULTS**

**LONG PROGRESSION FREE SURVIVAL**

**PFS, median (95% CI)**
11.7 months (8.1 – NR)

Median follow-up:
14.2 months (95% CI: 11.8 – 20.5)

Data Cut-off: October 15, 2018

Bagot M et al, ASH 2018
# Clinical Efficacy Results

## Subgroup Analysis

<table>
<thead>
<tr>
<th></th>
<th>All SS N=35</th>
<th>SS without LCT N=28</th>
<th>Prior treatment with mogamulizumab N=7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best global response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- CR</td>
<td>2 (5.7%)</td>
<td>2 (7.1%)</td>
<td>0</td>
</tr>
<tr>
<td>- PR</td>
<td>13 (37.2%)</td>
<td>13 (46.5%)</td>
<td>3 (42.9%)</td>
</tr>
<tr>
<td>- SD</td>
<td>16 (45.7%)</td>
<td>11 (39.3%)</td>
<td>3 (42.9%)</td>
</tr>
<tr>
<td>- PD</td>
<td>4 (11.4%)</td>
<td>2 (7.1%)</td>
<td>1 (14.2%)</td>
</tr>
<tr>
<td><strong>Duration of Response</strong></td>
<td>13.8 (7.2 – NR)</td>
<td>13.8 (7.2 – NR)</td>
<td>13.8 (7.2 – NR)</td>
</tr>
<tr>
<td><strong>Progression Free Survival</strong></td>
<td>11.7 (8.1 – NR)</td>
<td>12.8 (8.2 – NR)</td>
<td>16.8 (8.1 – NR)</td>
</tr>
</tbody>
</table>

* Median (95% CI)

Data Cut-off: October 15, 2018

LCT: Large Cell Transformation tested centrally on frozen tissue
QUALITY OF LIFE
SKINDEX29 (N = 35)

Data Cut-off: October 15, 2018

Bagot M et al, ASH 2018
QUALITY OF LIFE
PRURITUS VISUAL ANALOGUE SCALE SCORE (N = 35)

Data Cut-off: October 15, 2018
EXPLORATORY BIOMARKERS
CHANGES IN KIR3DL2 EXPRESSING CELLS IN SKIN

Patient 11-005, global partial response since W10 lasting 1 year and 8 months

Baseline
KIR3DL2: 52%

Week 5
KIR3DL2: 4.4%

Baseline
mSWAT: 80.5/1/0

Week 64
mSWAT = 5.2/0/0

^ 77 y old woman, received 6 prior lines of systemic therapies including Bex, IFN, HDAC and Mogamulizumab
Global PR since week 10 (starting dose: 0.05 mg/kg)

Bagot M et al, ASH 2018
EXPLORATORY BIOMARKERS
CHANGES IN TUMOR CELLS AND KIR3DL2 IN BLOOD

Aberrant cells

KIR3DL2+ CD4+ T cells

Patient 01-036,
ongoing complete response > 1 year

Number CD7- or CD26- CD4+ T cells/µL

Number KIR3DL2+ CD4+ T cells/µL

CR+PR (mean of 14 SS pts)
SD (mean of 16 SS pts)
PD (mean of 4 SS pts)

CR+PR (mean of 15 SS pts)
SD (mean of 15 SS pts)
PD (mean of 4 SS pts)

Bagot M et al, ASH 2018
EXPLORATORY BIOMARKERS
REDUCTION IN KIR3DL2 / MRD AT WEEK 5 AND GLOBAL RESPONSE

Exploratory analysis unadjusted for possible confounders

Bagot M et al, ASH 2018
CONCLUSIONS

- IPH4102 is **safe and well tolerated** in heavily pretreated relapsed/refractory SS.
- IPH4102 shows impressive clinical activity, demonstrated by **high and durable response** rate and **long PFS**.
- IPH4102 **substantially improved QOL** even in patients with stable disease.
- Exploratory biomarker analyses show **relevant pharmacodynamics effects of IPH4102 in skin and in blood**. These results will be further evaluated in future studies.

Bagot M et al, ASH 2018
PHASE 2 STUDY (N≈250)

TELLOMAK: T-CELL LYMPHOMA ANTI-KIR3DL2 THERAPY

Sézary Syndrome
≥ 2 prior systemic therapies that must include mogamulizumab

Mycosis Fungoides
≥ 2 prior systemic therapies

Peripheral T Cell Lymphoma
≥ 1 prior systemic therapy including anthracycline-based chemo

IPH4102 single agent

IPH4102 + GEMOX

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All our patients and their families…