KIR2DL1,2,3
NKG2A
NKP46
KIR3DL2
MICA/B
CD73
CD39

NOVEL CHECKPOINTS IN IMMUNO-ONCOLOGY
FORWARD LOOKING STATEMENT

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INNATE PHARMA ACQUIRES FIRST-IN-CLASS ANTI-C5AR ANTIBODY
**ANTI-C5AR, A NOVEL THERAPEUTIC APPROACH IN IMMUNO-ONCOCOLOGY (IO)**

- Anti-C5aR (IPH5401) is a first-in-class therapeutic mAb targeting myeloid-derived suppressor cells (MDSC) and neutrophils in the tumor microenvironment
  - These cells suppress anti-tumor immune-responses
  - They are associated with resistance to checkpoint blockers

- New proprietary clinical-stage asset, with strategic fit to
  - Innate Pharma’s pipeline of mAbs designed to stimulate anti-tumor activities of NK and other immune cells
  - IPH’s pipeline of mAbs targeting the tumor microenvironment, boosted with clinical asset

- Trial initiation with IPH5401 in oncology expected in 2018
  - Favorable safety profile in single- and multi-dose Phase I trials in arthritis patients (Novo Nordisk A/S)
STRENGTHENING OF INNATE PHARMA’S PIPELINE OF FIRST-IN-CLASS MABS IN IO

Inflamed

- Checkpoint-inhibited T and NK cells
- No T or NK cells in tumor

Non inflamed

- T and NK cells suppressed or excluded

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**NK cell checkpoint**
- lirilumab

**NK and T cell checkpoint**
- monalizumab

**ADCC mAb**
- IPH4102

**MDSC**
- IPH5401

**ADCC mAb**
- IPH4301

**Adenosine pathway**
- IPH52 and IPH53

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Bispecific antibodies

Adapted from Hedge et al., Clin Cancer Res 2016
SUMMARY OF THE TRANSACTION

• Agreement granting IPH full worldwide exclusive rights to develop and commercialize a first-in-class clinical-stage anti-C5aR antibody

• Upfront payment of €40M
  > €37.2M in new Innate shares and €2.8M in cash
  > The number of shares to be issued will be based on the 10 days VWAP* preceding closing, subject of a minimum of 2,700,000 shares and to a maximum of 3,500,000 shares
  > After the closing of the transaction, Novo Nordisk A/S’s stake in Innate Pharma will increase from 10.3% currently to between 14.6% to 15.8%, depending on this average trading price
  > Closing expected by July 12, 2017

• Development, regulatory and sales milestones payments up to €370M

• Double-digit royalties on net sales

* VWAP: volume weighted average price
RATIONALE FOR TARGETING MDSC AND C5AR IN ONCOLOGY
IPH5401, A FIRST-IN-CLASS MAB
MECHANISM OF ACTION

• IPH5401 is a fully human anti-C5aR blocking antibody
  > High affinity and high potency; no Fc-mediated depletion or agonist activity
• Has potential to enhance anti-tumor immunity across a range of tumor types
  > MDSC-targeting has proven effectiveness in a range of experimental models

MDSC/Neutrophils

C5aR receptor

CD8 or CD4 T cell

NK cell

C5a

Tumor spreading

Immunosuppression

MDSC mediate pro-tumoral inflammation and immune suppression

Activation of effector cells by C5aR-blockade

Tumor killing

Anti-C5aR

innate pharma
MDSC ARE ABUNDANT IN NUMEROUS CANCERS
MDSC AND NEUTROPHILS ARE OFTEN ASSOCIATED WITH A POOR PROGNOSIS

MDSC MAY RENDER PATIENTS REFRACTORY TO CHECKPOINT BLOCKERS

Hedge et al., Clin Cancer Res 2016
MDSC PROMOTE TUMOR GROWTH AND SUPPRESS ANTI-TUMOR IMMUNE RESPONSES

- MDSC and neutrophils suppress effector T and NK cells by the production of cytokines and induction of Tregs
- MDSC secrete pro-inflammatory and pro-angiogenic factors that promote tumor growth and metastasis
- C5a is a potent chemo-attractant and activator of MDSC and neutrophils

Adapted from Suzanne Ostrand-Rosenberg and Pratima Sinha, J Immunol 2009
RECENT DATA PROVIDE RATIONALE FOR C5AR-BLOCKADE IN ONCOLOGY

• C5a and its receptor are upregulated in several types of cancer$^{1,2}$
• C5aR mediates accumulation of MDSC in mouse tumors$^3$
• M2 macrophages express high levels of C5aR and respond strongly to C5a-induced chemotaxis$^4$
• C5aR signaling stimulate secretion of TGFβ by MDSC which suppress T and NK cells$^5,6$
• C5aR induces PD-L1 expression on monocytes$^2,7$
• C5aR depletion or pharmacological inhibitors slow tumor growth and synergize with anti-PD1$^3,8,9,10$

C5A AND ITS RECEPTOR ARE UPREGULATED IN SEVERAL TYPES OF CANCER

• C5aR appears to be highly express in several cancer types with abundant MDSC

1 IHC for C5aR in colorectal and esophagus

2 Elevated levels of C5a in circulation of NSCLC patients

1 Hidetoshi Nitta et al., Clin Cancer Res, 2013; 2 Corrales et al J. Immunol 2012
C5AR KO MICE: FEWER AND LESS FUNCTIONAL MDSCs, AND REDUCED TUMOR GROWTH

C5aR KO mice have reduced numbers of tumor infiltrating MDSCs

MDSCs from C5aR KO mice have reduced tumor growth

MDSCs from C5aR KO mice produce reduced levels of ROS and RNS

MDSCs from C5aR KO mice are unable to suppress T cell proliferation

Markiewski et al., Nat Immunol., 2008
HUMAN M2 MACROPHAGES EXPRESS HIGH LEVELS OF C5AR AND RESPOND STRONGLY TO C5A-INDUCED CHEMOTAXIS

M1 and M2 migrations were performed individually and quantified with Cell Titer Glo
C5A BLOCKADE CONTROLS THE GROWTH OF ESTABLISHED LUNG TUMORS, AND SYNERGIZES WITH ANTI PD-1

393P model: Kras driven highly aggressive lung adenocarcinoma

Similar efficacy observed in a model of Lewis lung cancer

Ajona D et al; Cancer Discovery 2017
CONCLUSIONS

• Tumor microenvironment and infiltration by immunosuppressive cells (e.g. MDCS) are increasingly viewed as a key tumor escape mechanism

• Anti-C5aR is a novel approach for reducing infiltration and activation of MDSC
  > Inhibits both MDSC and suppressor neutrophils

• IPH5401 is a first-in-class, clinical-stage anti-C5aR blocking antibody
  > Favorable safety profile in single- and multi-dose Phase I trials in arthritis patients
  > In-house validation in cancer
  > Potential for single-agent and combination with PD-1 checkpoint blockade

• Trials initiation with IPH5401 in oncology expected in 2018
# BROAD, INNOVATIVE AND DIVERSIFIED PORTFOLIO

<table>
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<tr>
<th>CLINICAL PROGRAM</th>
<th>TARGET</th>
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<tr>
<td><strong>Lirilumab</strong></td>
<td>KIR2DL-1,-2,-3</td>
<td>Squamous cell carcinoma of the head and neck (SCCHN) Solid and hematological tumors - Multiple combinations</td>
<td>Randomized Phase I/II Phase I &amp; II trials</td>
<td>Licensed to Bristol-Myers Squibb</td>
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<td><strong>Monalizumab</strong></td>
<td>NKG2A</td>
<td>Solid and hematological tumors - Single agent and multiple combinations</td>
<td>Phase I/II trials</td>
<td>Co-development with AstraZeneca</td>
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<td><strong>IPH4102</strong></td>
<td>KIR3DL2</td>
<td>Cutaneous T-cell lymphomas (CTCL)</td>
<td>Phase I including cohort expansion</td>
<td>Innate Pharma</td>
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<tr>
<td><strong>IPH5401</strong></td>
<td>C5aR</td>
<td>Cancer</td>
<td>Trials to start in 2018</td>
<td>Innate Pharma</td>
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<tr>
<th>PRECLINICAL PROGRAM</th>
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<tr>
<td><strong>IPH4301</strong></td>
<td>MICA/B  Cancer</td>
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<td><strong>IPH52</strong></td>
<td>CD39     Cancer</td>
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<tr>
<td><strong>IPH53</strong></td>
<td>CD73     Cancer</td>
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BIBLIOGRAPHY: TARGETING MDSC

• The role of myeloid cells in cancer therapies (Engblom et al. Nat. Rev. Cancer 2016)

• Eradication of metastatic mouse cancers resistant to immune checkpoint blockade by suppression of myeloid-derived cells (Kim et al. PNAS 2014)

• Prostate: Effective combinatorial immunotherapy for castration-resistant prostate cancer (Lu et al. Nature 2017)

• Breast and melanoma: Overcoming resistance to checkpoint blockade therapy by targeting PI3Kγ in myeloid cells. (De Henau O et al., Nature 2016)

• Pancreatic: CSF1/CSF1R Blockade Reprograms Tumor-Infiltrating Macrophages and Improves Response to T Cell Checkpoint Immunotherapy in Pancreatic Cancer Models. Yu Zhu et al., Cancer res (2014)

BIBLIOGRAPHY: C5AR IN CANCER

• Complement C5a Receptor (C5aR) promotes myeloid-derived suppressor cells (MDSC) and reduces T cells (Markiewski et al Nature Immunology 2008)

• C5aR ko mice exhibit reduced tumor growth and in mouse TC1 solid tumor model, single-agent C5aR antagonist peptide inhibited tumor growth, w efficacy similar to Paclitaxel (Markiewski et al Nature Immunology 2008)

• C5aR blockade by antagonist peptide inhibited accumulation of MDSC and reduced metastasis in mice. C5a upregulated in patients with NSCLC. (Corrales et al. J. Immunol 2012)

• In three mouse models of lung cancer, C5aR antagonist peptide inhibited tumor growth and synergized with anti- PD-1 (Ajona et al.Cancer Discovery 2017)

• C5aR can be expressed on CD8 T cells and blockade enhances anti-tumor activity (Wang et al, Cancer Discovery 2016 – commentary by Hwu et al in same issue)

C5A/C5AR PATHWAY IN MDSCs AND CANCER

<table>
<thead>
<tr>
<th>Neutrophils</th>
<th>MDSC</th>
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<tbody>
<tr>
<td>CD11b+</td>
<td>CD11b+</td>
</tr>
<tr>
<td>CD14-</td>
<td>CD14+</td>
</tr>
<tr>
<td>CD15+</td>
<td>CD15-</td>
</tr>
<tr>
<td>Ly6G+</td>
<td>Ly6G-</td>
</tr>
<tr>
<td>Ly6C-</td>
<td>Ly6C+</td>
</tr>
<tr>
<td>CD33-</td>
<td>CD33+</td>
</tr>
<tr>
<td><strong>C5aR+</strong></td>
<td><strong>C5aR+</strong></td>
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C5aR is one of the few markers expressed on both Neutrophils and MDSCs

Recruitment of Neutrophils and MDSCs

- Complement accumulation
- Recruitment of Neutrophils and MDSCs
- Immune suppression
- Neoangiogenesis
- Tumor cell migration and invasiveness

Decreased trafficking of Neutrophils and MDSCs

Influx of CD8+ T Cells

- Immune suppression and inflammation
- Angiogenesis
- Tumor cell migration and invasiveness

Anti-C5aR

**C5a**  **C5aR**  Tumor Cell  Cancer-Associated Fibroblast (CAF)  Neutrophils  MDSC  CD8+ T-cells  PD-1
C5aR FUNCTIONS

Monocytes and macrophages
- chemotaxis
- phagocytosis ↑
- Cytokine/chemokine release ↑
  - TNFα, IL-1 and IL-6 ↑
  - Synergy with TLR ligands and IC
- CR1, -3 and activating FcyRs ↑

Neutrophils
- adhesion CD11b/CD18↑ = CD62L↓
- transendothelial migration MMP9
- chemotaxis
- phagocytosis ↑
- release of granules ↑
- apoptosis ↓
- NETosis

Dendritic cells
- chemotaxis
- maturation ↑

Eosinophils
- chemotaxis
- release of granules ↑

Mast cells
- chemotaxis
- histamine release ↑
- IL-1, -6, -8 and -17A

Basophils
- histamine release ↑
C5a INDUCES PD-L1 EXPRESSION AND CYTOKINE RELEASE IN MONOCYTES

C5a induces PD-L1 expression on human monocytes via C5aR1 but not C5aR2

C5a induces the production of immunosuppressive cytokines in human monocytes

C5A BLOCKADE DECREASES LUNG CANCER GROWTH AND METASTASIS, AND SYNERGIZES WITH ANTI PD-1

393 P model: Kras driven highly aggressive lung adenocarcinoma

Prevention of multiorgan metastasis

Similar efficacy observed in a model of Lewis lung cancer

Ajona D et al; Cancer Discovery 2017