Disclosures

• Innate-Pharma, co-founder + CSO
The Immuno-Oncology Revolution

Immune Checkpoints Inhibitors

Anti-CTLA4
- Ipilimumab (IgG1, YERVOY, BMS)
- Tremelimumab (IgG2, ASTRAZENECA)

Anti-PD-1
- Nivolumab (IgG4, OPDIVO, BMS)
- Pembrolizumab (IgG4, KEYTRUDA, MERCK)
- Cemiplimab (IgG4, LIBTAYO, SANOFI/REGENERON)

Anti-PD-L1
- Avelumab (IgG1, BAVENCIO, MERCK KGaA/PFIZER)
- Durvalumab (IgG1, IMFINZI, ASTRAZENECA)
- Atezolumab (IgG1, TECENTRIQ, GENENTECH/ROCHE)
The Immuno-Oncology Revolution

- Understand the resistance to Immune Checkpoint Inhibitors
- Increase the fraction of patients sensitive to IO treatments
- Decrease toxicity
The Immuno-Oncology Revolution

- Understand the resistance to Immune Checkpoint Inhibitors
- Increase the fraction of patients sensitive to IO treatments
- Decrease toxicity
- Identify new targets (cells and molecules)
- Identify biomarkers
A pivotal role of T cells in tumor immunity
T cells are not autonomous in their anti-tumor functions.
A pivotal role of innate immunity to mount anti-tumor T cell responses

TYPE I IFNs

cGAS STING

DC / Macrophage / Endothelial cell

Tumor-specific CD8 T cell

NK cell

Tumor Microenvironment

DNA cGAMP

XCL1/CCL5/FLT3L

CXCL9/CXCL10

cDC1

Tumor cell

KILLING

KILLING
**Innate Lymphoid cells**

<table>
<thead>
<tr>
<th>Stimuli</th>
<th>Mediators</th>
<th>Immune function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumors, intracellular microbes (Virus, bacteria, parasites)</td>
<td>NK, ILC1</td>
<td>Type 1 immunity (Macrophage activation, cytotoxicity)</td>
</tr>
<tr>
<td>Large extracellular parasites and allergens</td>
<td>ILC2</td>
<td>Type 2 immunity (Alternative macrophage activation)</td>
</tr>
<tr>
<td>Mesenchymal organizer cells (Retinoic acid, CXCL13, RANK-L)</td>
<td>LTi</td>
<td>Formation of secondary lymphoid structures</td>
</tr>
<tr>
<td>Extracellular microbes (Bacteria, fungi)</td>
<td>ILC3</td>
<td>Type 3 immunity (Phagocytosis, antimicrobial peptides)</td>
</tr>
</tbody>
</table>

Vivier et al., *Nature Immunol.* 2008
Vivier et al., *Science* 2011
Vivier et al., *Cell* 2018
Targeting Innate Immunity in Cancer

• Targeting NK cells
  – Targeting inhibitory NK cell surface receptors
  – Targeting activating NK cell surface receptors
Targeting Innate Immunity in Cancer

• Targeting NK cells
  – Targeting inhibitory NK cell surface receptors: NKG2A
  – Targeting activating NK cell surface receptors
Blocking anti-NKG2A mAb: a novel immune checkpoint inhibitor in cancer immunotherapy

MONALIZUMAB (IPH2201) IS A FIRST-IN-CLASS ANTI-NKG2A HUMANIZED IGG4 BLOCKING MAB
Monalizumab is a novel checkpoint inhibitor promoting anti-tumor immunity by enhancing the activity of both T and NK cells, which may complement the activity of the first generation of active immunotherapies against cancer.

André et al., Cell 2018
Monalizumab: a large spectrum immune checkpoint inhibitor

Monalizumab blocks NKG2A/HLA-E inhibitory pathway to unleash NK and T cell activity

Combined blockade of non-redundant checkpoint pathways to unleash NK and T cells

Durvalumab stops PD-L1 from binding to PD-1 to turn NK and T cells off
Monalizumab: a large spectrum immune checkpoint inhibitor
Targeting Innate Immunity in Cancer

• Targeting NK cells
  – Targeting inhibitory NK cell surface receptors: NKG2A
  – Targeting activating NK cell surface receptors
NKp46 is a conserved activating cell surface receptor

Comparing mouse and human data

(65-75 Mya differences between mice and humans)
Multifunctional antibody technology engaging NK cells in oncology

Innovative multifunctional antibody technology for engaging NK cells to kill tumor cells through activating receptors expressed on NK cells

- Co-engaging CD16 and NKp46 on NK cells
- Stimulates NK cells instead of T cells
- Expect improved benefit-risk profile
- Opportunities for development in solid tumors (higher dosing)
- New IgG-fc based format expected to solve main PK and CMC issues
NKp46 is expressed at the tumor bed

Density of NKp46+ cells

Cells / mm²

Density of NKp46+ cells

CD8 / Hematoxylin

NKp46 / Hematoxylin

Colon

Head & Neck

Kidney

Liver

Lung

Pancreas

Stomach

n=103

n=68

n=75

n=106

n=45

n=77

n=76

50 µm
NKp46 NK cell engagers in oncology

- Correct chain pairing driven by affinity
- 100% antibody sequences
- Binding to Protein-A and FcRn
- Monovalent binding to NKp46

- FcγR binding options
  - NKp46 only: NKCE-1
  - NKp46 + CD16: NKCE-2
  - NKp46 + ADCC enh.: NKCE-3
NKp46 NK cell engagers in oncology
Bispecific NKCEs promote tumor control *in vivo*

**Injection**
5x10^6 Raji cells S.C.

**Randomization**
~ 100 mm^3

**Treatment start**
Day 9

**F6**
F6

**Day 9**
Day 16
Day 23

---

**Mean tumor volume (mm^3)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Tumor Volume (mm^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC((Fc)/CD20-F6 (6.25 mg/kg)</td>
<td>1,500</td>
</tr>
<tr>
<td>NKp46/(Fc)/CD20-F6 (6.25 mg/kg)</td>
<td>1,000</td>
</tr>
<tr>
<td>NKp46/(Fc)/CD20-F6 (0.25 mg/kg)</td>
<td>500</td>
</tr>
<tr>
<td>NKp46/(Fc)/CD20-F6 (6.25 mg/kg)</td>
<td>0</td>
</tr>
<tr>
<td>IC((Fc)/CD20-F6 (6.25 mg/kg) NK depleted</td>
<td>ns</td>
</tr>
</tbody>
</table>

---

**Time (days)**

- 10
- 20
- 30

---

**Mean tumor volume (mm^3)**

- **IC((Fc)/CD20-F6 (6.25 mg/kg))**: 1,500
- **NKp46/(Fc)/CD20-F6 (6.25 mg/kg)**: 1,000
- **NKp46/(Fc)/CD20-F6 (0.25 mg/kg)**: 500
- **NKp46/(Fc)/CD20-F6 (6.25 mg/kg) NK depleted**: 0
- **IC((Fc)/CD20-F6 (6.25 mg/kg) NK depleted**: ns

---

**Statistical Significance**

- *******: Significant
- **ns**: Not significant
Bispecific NKCEs promote tumor control *in vivo*

Bispecific NKCE treatment promotes the NK cell infiltration and/or proliferation within tumors.
Trifunctional NKCEs promoting ADCC are more efficient than bispecific mAbs
Trifunctional NKCEs are more potent than the combination of molecules activating NKp46 and CD16 separately.
Trifunctional NKCEs do not mediate off-target killing nor NK-vs-NK toxicity.
NKp46 NK cell engagers

Innovative multifunctional antibody technology for engaging NK cells to kill tumor cells through activating receptors expressed on NK cells

- Co-engaging CD16 and NKp46 on NK cells
- Stimulates NK cells instead of T cells
- Expect improved benefit-risk profile
- Opportunities for development in solid tumors (higher dosing)
- First-in-class agonist anti-NKp46 mAbs
- New IgG-fc based format expected to solve main PK and CMC issues

Gauthier et al., in press
Next generation IO: 3 strategic key pillars to harness the potential of immunity

1. Immune Checkpoints MONALIZUMAB

2. Tumor Targeting NK CELL ENGAGERS
Next generation IO: 3 strategic key pillars to harness the potential of immunity

1. Immune Checkpoints MONALIZUMAB
2. Tumor Targeting NK CELL ENGAGERS
3. Tumor microenvironment ADENOSINE
The adenosine pathway is immunosuppressive
CD39 is upregulated on TILs

A

NK cells

CD8+ T cells

CD4+ T cells

CD4+ Treg

B

Tumor tissue

CD39+ (%)

CD39+PD-1+ (%)

Expression on vascular endothelial cells and immune cells
IPH52 (anti-CD39) enhances ATP-mediated DC activation

**A**

![Graph showing DC activation](image)

- **DC Activation**
  - Y-axis: Median of Fluorescence
  - X-axis: ATP (mM)
  - Conditions: IPH52, IPH53, No Ab

**B**

![Bar graph showing T cell proliferation](image)

- **T cell proliferation**
  - Y-axis: Proportion of Proliferating T Cells (%)
  - X-axis: No Ab, IPH52, IPH53

**Diagram**

- **Monocyte-derived DC**
  - CD39 or CD73 mAbs
  - ATP
  - Allogeneic CD4+ T cells
  - 24h, 37°C
  - Phenotypic analysis (Flow cytometry)
  - CTV dilution (Flow cytometry)
IPH5201 (anti-CD39) restores T cell proliferation
IPH52 (CD39) enhances tumor control in human CD39 KI mice

MCA205 cells 1x10^6

PBS + control Ab

Days

Tumor volume (mm^3)

PBS + control Ab

PBS + IPH52

Days

Oxaliplatin 10 mg/kg, IP

D7 D11 D14 D19 D22 D26 D29

D5 or D12 or D14

Oxaliplatin 10 mg/kg, IP

Days

Oxaliplatin + control Ab

Days

Oxaliplatin + IPH52

Days

Survival

Percent survival

Time (day)

Oxaliplatin

IPH52 (anti-CD39)

Control

IPH52 + Oxaliplatin

Survival

Days

PBS + control Ab

PBS + IPH52

Oxaliplatin + control Ab

Oxaliplatin + IPH52

Percent survival

Time (day)

Survival

Percent survival

Time (day)

Survival

Percent survival

Time (day)
The adenosine pathway
The adenosine pathway
High efficacy of IPH53, a blocking anti-CD73 mAb

Cell-associated CD73

Soluble CD73

Enzyme inhibition (%)

AMP (units x 10^6)

AMP (units x 10^6)

AMP (units x 10^6)

Ab (µg/ml)

Ab (µg/ml)

Ab (µg/ml)
High efficacy of IPH53, a blocking anti-CD73 mAb
IPH53 blocks enzyme activity by constraining CD73 in an intermediate conformation

- The negative staining of the CD73-IPH53 complex analyzed by electron microscopy revealed that IPH53 mAb interacts with CD73 mainly in a 1:1 stoichiometry (upper panel).
- As shown on the CD73/IPH53 crystal (middle panel), IPH53 F(ab) orientation on the N-terminal domain of CD73 is compatible with an intra-dimer binding mode as it is located right on the apex of the molecule, in contrast to Medi9447 and BMS mAbs whose epitopes are eccentric and that are described to interact with CD73 in an inter-dimer mode.
- Our data support a model for the mode of action of IPH53, as which the intact mAb constraints CD73 in an intermediate state in which AMP could not be hydrolyzed (lower panel).
The combination of IPH52 and IPH53 releases ATP-mediated suppression of T cells from healthy donors and cancer patients

• When used in combination at inefficient suboptimal doses, the anti-CD39/CD73 mAbs acted in synergy to abrogate the suppressive effect of ATP and to promote the proliferation of T cells from healthy donors (purple lines to be compared to blue and red lines and dots) (upper panel)

• Similar results were obtained for T cells from breast cancer patient PBMC (lower panel)

• These data show that the concomitant blockade of CD39 and CD73 enzyme abolishes Ado-mediated T-cell inhibition
The adenosine pathway is immunosuppressive

ATP: Adenosine Triphosphate
AMP: Adenosine Monophosphate
The adenosine pathway can be controlled.
Next generation IO: 3 strategic key pillars to harness the potential of immunity

1. Immune Checkpoints MONALIZUMAB
2. Tumor Targeting NK CELL ENGAGERS
3. Tumor microenvironment ADENOSINE

innate pharma
THANKS to PATIENTS and their FAMILIES

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Nathalie BONNEFOY, IRCM, Montpellier
Co-expression of NKG2A and PD-1 in TILs

CD8⁺ T cells

<table>
<thead>
<tr>
<th></th>
<th>Spleen</th>
<th>Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NKG2A</td>
<td>3.3</td>
<td>26.1</td>
</tr>
<tr>
<td>PD-1</td>
<td>0.2</td>
<td>33.8</td>
</tr>
<tr>
<td>Percent</td>
<td>96.0</td>
<td>39.0</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>1.1</td>
</tr>
</tbody>
</table>

André et al., Cell 2018
HLA-E expression in human solid tumors

HLA-E

PD-L1

André et al., Cell 2018
Combination of monalizumab and durvalumab

- Tumor infiltrating NK and CD8\(^+\) T cells expressing NKG2A and/or PD-1 are present in several cancer types.
- HLA-E is expressed by tumor cells in the large majority of solid tumors.
- Blocking both NKG2A/HLA-E and PD-1/PD-L1 pathways can enhance responses of NK and CD8\(^+\) T cells.

André et al., Cell 2018
Anti-NKG2A as a novel immune checkpoint inhibitor in cancer

NK cell and T cell inhibition by NKG2A & PD-1

Activation by NKG2A & PD-L1 blockade

In vitro data support the rationale for ongoing clinical trial investigating the combination monalizumab/durvalumab
Monalizumab potentiates cetuximab-induced ADCC

ADCC enhancement by NKG2A blockade

Cetuximab (Ctx): anti-EGFR
Monalizumab (Mona): anti-NKG2A
Phase II clinical trial in recurrent or metastatic SCCHN

### KEY RESULTS

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>1 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>Partial response (PR)*</td>
<td>10 (25%)</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>22 (55%)</td>
<td></td>
</tr>
<tr>
<td>Overall Response Rate (ORR)</td>
<td>27.5% [16.1-42.8]</td>
<td></td>
</tr>
<tr>
<td>Median PFS</td>
<td>5.0 months [3.7-6.9]</td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>10.3 months [7.3.-NR]</td>
<td></td>
</tr>
</tbody>
</table>

### Safety data:
- Good safety profile of the combination
- No potentiation of the cetuximab related AEs by monalizumab

Cutoff data: Aug 31, 2018
IPH52 blocks CD39 in human CD39 preclinical mouse model

- We generated a human CD39 knock-in mice by replacing the mouse CD39 by human CD39 protein using a knock-out/knock-in (KI) molecular biology strategy.
- In contrast to splenocytes from mouse CD39 KO mice, splenocytes from human CD39 KI mice are as efficient as WT mice to hydrolyze exogeneous ATP.
- Murinized IPH52 (IPH52 with a mouse Fc silent IgG1 isotype) mouse treatment prevented ex vivo ATP hydrolysis by human CD39 KI cells (blue histograms).
- Similar results were obtained with spleen dissociation supernatants suggesting that moIPH52 was able to block both membrane associated and soluble CD39 enzyme activity.
Trifunctional NKCEs promoting ADCC are more efficient than bispecific mAbs in vivo.

- F6 (Fc-silent)
- F5 (Normal Fc)

Randomization ~ 100 mm³
Injection 5x10⁶ Raji cells S.C.
Treatment start (Day 8) (Day 17)

Tumor volume (mm³)

- NKp46/(Fc)/CD20-F6 (6.25 mg/kg)
- NKp46/Fc/CD20-F5 (6.25 mg/kg)
- IC/(Fc)/CD20-F6 (6.25 mg/kg)
- Obinutuzumab (6.25 mg/kg)

Days (post-engraftment)

0 5 10 15 20 25 30

1,500 1,000 500 0

ns
Trifunctional NKCEs promoting ADCC are more efficient than bispecific mAbs in vivo.
NKp46 expression is not downregulated in cancer

A

Density plots

Heatmaps

Blood

Cluster 1
Cluster 2

Tumor

Cluster 1
Cluster 2

Heatmaps

% among NK cells

Cluster # 1
Cluster # 2

NKp46 expression is not downregulated in cancer
Qa-1<sup>b</sup> expression blocks the anti-tumor efficacy of NK and CD8<sup>+</sup> T cells
Co-expression of NKG2A and PD-1

A20 tumor-bearing BALB/c mice

### NK cells

<table>
<thead>
<tr>
<th></th>
<th>Spleen</th>
<th>Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NKG2A+PD1-</td>
<td>0.4 ± 0.2</td>
<td>0.3 ± 0.3</td>
</tr>
<tr>
<td>NKG2A+PD1+</td>
<td>0.1 ± 0.1</td>
<td>0.5 ± 0.5</td>
</tr>
<tr>
<td>NKG2A-PD1-</td>
<td>38.7 ± 6.0</td>
<td>37.9 ± 6.1</td>
</tr>
<tr>
<td>NKG2A-PD1+</td>
<td>39.4 ± 1.3</td>
<td>37.1 ± 3.4</td>
</tr>
</tbody>
</table>

### CD8+ T cells

<table>
<thead>
<tr>
<th></th>
<th>Spleen</th>
<th>Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NKG2A+PD1-</td>
<td>60 ± 0.4</td>
<td>61.9 ± 2.9</td>
</tr>
<tr>
<td>NKG2A+PD1+</td>
<td>0.5 ± 0.3</td>
<td>0.5 ± 0.7</td>
</tr>
<tr>
<td>NKG2A-PD1+</td>
<td>0.1 ± 0.1</td>
<td>0.5 ± 0.6</td>
</tr>
<tr>
<td>NKG2A-PD1+</td>
<td>39.4 ± 1.3</td>
<td>37.1 ± 3.4</td>
</tr>
<tr>
<td>NKG2A-PD1-</td>
<td>2.2 ± 0.9</td>
<td>23.4 ± 12.1</td>
</tr>
<tr>
<td>NKG2A-PD1+</td>
<td>3.9 ± 2.1</td>
<td>21.1 ± 10.0</td>
</tr>
<tr>
<td>NKG2A-PD1+</td>
<td>95.0 ± 0.8</td>
<td>53.3 ± 20.9</td>
</tr>
</tbody>
</table>

**Legend:**
- **Blue**: NKG2A+PD1-
- **Light Blue**: NKG2A+PD1+
- **Gray**: NKG2A-PD1-
- **Pink**: NKG2A-PD1+
The combined blockade of NKG2A and PD-1/PD-L1 promotes anti-tumor immunity

A20 tumor-bearing BALB/c mice
Combined blockade of NKG2A and PD-1/PD-L1 promotes anti-tumor immunity in RMA Rae-1β tumor-bearing mice.

RMA Rae-1β tumor-bearing C57BL/6 mice treated with anti-PD-L1 and anti-NKG2A mAbs.
Combined blockade of NKG2A and PD-1/PD-L1 promotes anti-tumor immunity in RMA Rae-1β tumor-bearing mice

RMA Rae-1/β tumor-bearing C57BL/6 mice treated with anti-PD-L1 and anti-NKG2A mAbs
Combined blockade of NKG2A and PD-1/PD-L1 promotes anti-tumor immunity in RMA Rae-1β tumor-bearing mice.
NKG2A expression by TILs in humans
Monalizumab unleashes human CD8\(^+\) T cell function \textit{in vitro} alone and with durvalumab

CD8\(^+\) T cells cultured in vitro with monocytes, flu peptide and IL-15 (day 10)

Flu-specific CD8\(^+\) T cells challenged with flu peptide-pulsed K562 cells expressing PD-L1, HLA-E and HLA-A2
Monalizumab unleashes human NK cell function in vitro alone and with durvalumab

NK cells stimulated in vitro with IL-15 for 9 days
Trifunctional NKCEs promoting ADCC are more efficient than bispecific mAbs
**NKp46 NK cell engagers in oncology**

**Solid tumor model**

- Injection of 5x10⁶ Raji cells S.C. (Day 9)
- Randomization ~ 100 mm³
- Treatment start (Day 16)
- F6 (Day 23)

![Graph showing mean tumor volume over time for different treatments.](chart)

- IC/(Fc)/CD20-F6 (6.25 mg/kg)
- NKp46/(Fc)/CD20-F6 (6.25 mg/kg)
- NKp46/(Fc)/CD20-F6 (0.25 mg/kg)

**Significance:**
- **ns**
- ****
NKp46 NK cell engagers in oncology

Solid tumor model

- **Randomization**: ~100 mm³
- **Injection**: 5x10⁶ Raji cells S.C.
- **Treatment start**: (Day 8) (Day 17)

**Tumor volume (mm³)**
- NKp46/(Fc)/CD20-F6 (6.25 mg/kg)
- NKp46/Fc/CD20-F5 (6.25 mg/kg)
- IC/(Fc)/CD20-F6 (6.25 mg/kg)
- Obinutuzumab (6.25 mg/kg)

**Graph**
- Days (post-engraftment)
- Tumor volume (mm³)
  - 5
  - 10
  - 15
  - 20
  - 25
  - 30

**Legend**
- NKp46/(Fc)/CD20-F6 (6.25 mg/kg)
- NKp46/Fc/CD20-F5 (6.25 mg/kg)
- IC/(Fc)/CD20-F6 (6.25 mg/kg)
- Obinutuzumab (6.25 mg/kg)
NKp46 NK cell engagers in oncology

Invasive tumor model

Survival (%)

Days (post cell injection)

0 20 40 60 0 20 40 60 0 20 40 60

0 50 100 0 50 100 0 50 100

Injection 5x10^6 Raji cells I.V.

Day 0 Day 1

0.8 µg/kg

4 µg/kg

20 µg/kg

**

 ****

**

****

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NKp46/Fc/CD20-F5

IC/Fc/CD20-F6

Obinutuzumab

Gauthier et al.