Anti-NKG2A mAb is a checkpoint inhibitor that promotes anti-tumor immunity by unleashing both T and NK cells

Eric Vivier
Disclosures

• Innate-Pharma, co-founder + CSO
The immuno-oncology revolution

- Shift of cancer treatment from a focus on the tumor to the host with the development of various forms of immune-based therapies that mobilize the immune system to promote or restore an effective antitumor immune response

- Therapeutic blocking antibodies that release immune inhibitory ‘checkpoints’ (immune checkpoint inhibitors, ICIs).
The immuno-therapy revolution

The dynamic equilibrium between activating and inhibitory receptors
Various shades of immuno-therapies - I

Blocking the inhibition

Effector immunocytes

Tumor cells

Immune Checkpoint Inhibitor

Blocking the inhibition
The Immuno-Oncology Revolution

Immune Checkpoint Inhibitors

• anti-CTLA-4
  > Ipilimumab (YERVOY, BMS)
  > Tremelimumab (MEDIMMUNE-ASTRAZENECA)

• anti-PD-1
  > Nivolumab (OPDIVO, BMS/ONO)
  > Pembrolizumab (KEYTRUDA, MERCK)

• anti-PD-L1
  > Avelumab (BAVENCIO, MERCK KGaA/PFIZER)
  > Durvalumab (IMFINZI, MEDIMMUNE-ASTRAZENECA)
  > Atezolizumab (TECENTRIQ, GENENTECH/ROCHE)
The Immuno-Oncology Revolution

Immune Checkpoint Inhibitors

- **anti-CTLA-4**
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What’s next in immuno-oncology?

- Understand the resistance to Immune Checkpoint Inhibitors
- Increase the fraction of patients sensitive to IO treatments
- Decrease toxicity
What’s next in immuno-oncology?

- 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
Immune checkpoints

Chiossone & Vivier, J. Exp. Med., 2017
Blocking anti-NKG2A mab as a novel immune checkpoint inhibitor in cancer immunotherapy?

MONALIZUMAB (IPH2201) IS A FIRST-IN-CLASS ANTI-NKG2A HUMANIZED IGG4 BLOCKING MAB
Qa-1\(^b\) expression blocks the anti-tumor efficacy of NK and CD8\(^+\) T cells

P. André et al.
Co-expression of NKG2A and PD-1

A20 tumor-bearing BALB/c mice

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>NK cells</th>
<th>CD8+ T cells</th>
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<tbody>
<tr>
<td></td>
<td>Spleen</td>
<td>Tumor</td>
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<tr>
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<tr>
<td>NKG2A+PD1−</td>
<td>0.4</td>
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<td>0.3</td>
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<tr>
<td>NKG2A+PD1+</td>
<td>0.1</td>
<td>0.3</td>
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<tr>
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<td>0.5</td>
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<tr>
<td>NKG2A−PD1−</td>
<td>39.4</td>
<td>37.1</td>
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<td>± 1.3</td>
<td>± 3.4</td>
</tr>
</tbody>
</table>

P. André, C. Soulas, C. Denis et al.
The combined blockade of NKG2A and PD-1/PD-L1 promotes anti-tumor immunity

A20 tumor-bearing BALB/c mice

P. André, C. Soulas, C. Denis et al.
HLA-E expression in human solid tumors

Pascale André et al.
CD8⁺, NKp46⁺ or NKG2A⁺ immune cells are present in several types of HLA-E-expressing solid cancers
Monalizumab unleashes human CD8$^+$ T cell function *in vitro* alone and with durvalumab

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**A**

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

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**B**

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 \textit{in vitro} alone and with durvalumab

\textbf{A}

\textbf{B}

\begin{align*}
\text{K562} & \quad \text{HLA-E} \\
\text{K562 HLA-E} & \quad \text{mona} \\
\end{align*}

\textit{Resting NKG2A\textsuperscript{+} NK cells}

\begin{align*}
\text{K562} & \quad \text{HLA-E} \\
\text{K562 HLA-E} & \quad \text{mona} \\
\end{align*}

\textit{NK cells stimulated in vitro with IL-15 for 9 days}
Combination of monalizumab and durvalumab in cancer immunotherapy

• 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
Anti-NKG2A as a novel immune checkpoint inhibitor in cancer

In vitro data support the rationale for ongoing clinical trial investigating the combination monalizumab/durvalumab (NCT02671435)
Can the NKG2A immune checkpoint blockade potentiate ADCC?
Can the NKG2A immune checkpoint blockade potentiate cetuximab-induced ADCC in head and neck cancer?

Cetuximab (Ctx): anti-EGFR
Monalizumab (Mona): anti-NKG2A

ADCC enhancement by NKG2A blockade?
SCCHN is one of the tumor types with high NK cell density

A

B

Pascale André et al.
Monalizumab enhances human NK cell-mediated ADCC

Cetuximab (Ctx): anti-EGFR
Monalizumab (Mona): anti-NKG2A
Monalizumab enhances human NK cell-mediated ADCC

Cetuximab (Ctx): anti-EGFR
Monalizumab (Mona): anti-NKG2A
Obinutuzumab (Obz): anti-CD20
NKG2A immune checkpoint blockade potentiates cetuximab-induced ADCC in head and neck cancer

- SCCHN are infiltrated by NK and CD8\(^+\) T cells expressing CD94/NKG2A
- HN tumor cells express HLA-E
- NKG2A blockade enhances cetuximab-mediated ADCC towards HN tumor cell lines
- These data support the rationale for investigating monalizumab in SCCHN patients and in combination with cetuximab in clinical trials (NCT02643550)
Phase II clinical trial in recurrent or metastatic SCCHN

Study Design and Dosing regimen

Multicenter, international (US and France), open label, single arm study to evaluate the antitumor activity of monalizumab in combination with cetuximab (NCT02643550).

Five doses of monalizumab (0.4, 1, 2, 4, 10 mg/kg every 2 weeks) in combination with the approved dosage of cetuximab (400 mg/m² load then 250 mg/m² weekly) were explored. The highest dose tested (10 mg/kg) was used for the phase II cohort expansion. A one-stage Fleming design with a futility analysis after the first 11 patients was used; the overall phase II study will include 40 patients.

Key eligibility criteria

- R/M SCCHN histologically confirmed, HPV (+) or HPV (-)
- Progression after platinum-based chemotherapy
- Maximum of 2 prior systemic treatment regimens for R/M disease; prior IO allowed; prior cetuximab allowed if used for the treatment of locally advanced disease, with no progressive disease for at least 4 months
Anti-tumor activity of monalizumab and cetuximab

As of March 9, 2018, 31 patients with R/M SCCHN were treated and evaluable for safety, 26 patients were evaluable for activity.

Baseline (July 2017)
Target lesion = 41mm
100% reduction in target lesion, no non-target lesions, no new lesions.

Under treatment (February 2018)
Target lesion = 0 mm
Anti-tumor activity of monalizumab and cetuximab

• This is the first report of activity of monalizumab, an anti-NKG2A monoclonal antibody, in combination with cetuximab in patients with SCCHN

• The safety profile is similar to the single agent experience with either agent. No potentiation of the cetuximab side-effects, no new or unusual safety signals were observed with the combination monalizumab and cetuximab

• According to the hypothesis of ORR of 25%, using 10% as inactivity cut-off rate, \( \alpha = 0.05 \), power 0.76, the predefined number of eight responses to declare the trial positive has been reached

• The trial is ongoing to enroll the 40 patients and allow long term assessment of duration of response, PFS and OS and final results will be presented with 40 patients
NKG2A targeting with monalizumab

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.
Various shades of immuno-therapies - I

Blocking the inhibition

Effector immunocytes

Tumor cells

Immune Checkpoint Inhibitor

Inhibitory Receptor

Activating Receptor
Various shades of immuno-therapies - II

Targeting the tumor via tumor antigens (Tag) with mAbs
Various shades of immuno-therapies - III

Blocking the inhibition and providing activation via anti-TAg mAbs
Pascale ANDRE
Agnès BOYER-CHAMMARD
Mathieu BLERY et al.
Cécile BONNAFOUS et al.
Caroline DENIS et al.
Pierre DODION
Laurent GAUTHIER et al.
Ariane MOREL et al.
Yannis MOREL
Romain REMARK et al.
Caroline SOULAS et al.
Robert ZERBIB

Anais BALSAMO
Adeline CRINIER
Bertrand ESCALIERE
Justine GALLUSO
Sophie GUIA
Yann KERDILES
Emilie NARNI-MANCINELLI
Margaux VIENNE
Christelle PIPEROGLOU
Frédéric VELY

Maria L. ASCIERTO
Hormas GHADially
Ronald HERBST
Robert W. WILKINSON

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Roger B. COHEN, Abramson Cancer Center, Philadelphia
Jérôme FAYETTE, Centre Léon Bérard, Lyon
Olivier LANTZ, Institut Curie, Paris
François ROMAGNE et al., MI-mAbs, Marseille
Anti-NKG2A mAb is a checkpoint inhibitor that promotes anti-tumor immunity by unleashing both T and NK cells.

Pascale André¹, Caroline Denis¹, Caroline Soulas¹, Clarisse Bourbon-Caillet¹, Julie Lopez¹, Thomas Arnoux¹, Mathieu Bléry¹, Cécile Bonnafous¹, Laurent Gauthier¹, Ariane Morel¹, Benjamin Rossi¹, Romain Remark¹, Violette Breso¹, Elodie Bonnet¹, Guillaume Habif¹, Sophie Guia², Ana Ines Lalanne³, Caroline Hoffmann³, Olivier Lantz³, Jérôme Fayette⁵, Agnès Boyer-Chammand¹, Robert Zerbib¹, Pierre Dodion¹, Hormas Ghadially⁶, Maria Jure-Kunkel⁷, Ronald Herbst⁷, Emilie Narni-Mancinelli², Roger B. Cohen⁸, Eric Vivier¹,²,⁹

¹ Innate Pharma, Marseille, France
² Aix Marseille Université, INSERM, CNRS, Centre d’Immunologie de Marseille-Luminy, Marseille, France
³ Unité INSERM U932, Immunité et Cancer, Institut Curie, Paris, France.
⁴ Service ORL et Chirurgie cervico-faciale, Institut Curie, Paris, France
⁵ Centre Léon Bérard, Lyon, France
⁶ MedImmune, Ltd, Aaron Klugg Building, Granta Park, Cambridge, UK
⁷ MedImmune, LLC, One MedImmune Way, Gaithersburg, MD 20817
⁸ Abramson Cancer Center, Philadelphia, PA, USA
⁹ Service d’Immunologie, Marseille Immunopole, Hôpital de la Timone, Assistance Publique-Hôpitaux de Marseille, Marseille, France