Targeting Checkpoint Receptors on Natural Killer Cells

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17 NOVEMBER, 2016
IMMUNO-ONCOLOGY: A REVOLUTION IN CANCER TREATMENT
NEED FOR NEW CHECKPOINTS AND NEW COMBINATIONS

• IO can lead to profound and durable responses in subsets of patients
  > Expected to impact all indications, all lines of treatments
• Led by checkpoint inhibitors, that “release the brake” on T cells
• But many patients fail to respond optimally
  > ~70-80% non-responders in head&neck, renal, lung, breast, and gastric cancer...

• Patient stratification
• Drugs w alternative MOAs
• Combination therapy
NATURAL KILLER (NK) CELL FUNCTIONS

- Directly kill tumor and virally infected cells
- Important role in controlling metastasis
- Produce cytokines (e.g. IFN-γ) that stimulate adaptive immunity
- Rapidly activated & potent responses
NK CELL ACTIVITY CONTROLLED BY ACTIVATING AND INHIBITORY RECEPTORS

NK cell

Tumor or infected target cell

Effector functions

CD16
NKG2D
NCRs
KIR

Ag
MICA
B7-H6, ??
HLA-C
TARGETING CHECKPOINTS IN IMMUNO-ONCOLOGY

NK cell

- Lirilumab, anti-KIR
- Monalizumab, anti-NKG2A
- NKp46-bispecific NK cell engagers
- IPH4102, anti-KIR3DL2
- IPH43, anti-MICA/B
- ATP pathway

Tumor antigen

- KIR3DL2
- MICA/B

Immune cell

- CD39
- CD73

Tumor cell

- KIR
- NKG2A
- NKp46
LIRILUMAB, FIRST-IN-CLASS ANTI-KIR ANTIBODY LICENSED TO BRISTOL-MYERS SQUIBB
THERAPEUTIC POTENTIAL OF NK CELLS DEMONSTRATED CLINICALLY
CONTROL OF RESIDUAL DISEASE IN ACUTE MYELOID LEUKEMIA (AML)

- Alloreactive NK cells can protect against tumor relapse, leading to improved survival in AML patients after haplo-identical HLA mismatch stem cell transplantation

Effects are:
- Durable
- Safe
- Mediated by NK cells
- Controlled by KIR

Ruggeri et al., Science, 2002 (not shown)
Ruggeri et al, Blood, 2007
AML relapse after haplo-identical stem cell transplantation

- Three types of KIR2DL(495,639),(681,678)
- Need for a cross reactive mAb

Donor NK cells

Patient AML blast

- Match
- Mismatch

KIR
LIRILUMAB IS A FIRST-IN-CLASS KIR CHECKPOINT INHIBITOR
MECHANISM OF ACTION AS SINGLE AGENT

- Fully human antibody (IgG4) blocking NK cell inhibitory receptor KIR2DL1,2,3
- Prevents interaction with HLA-C class I molecules to potentiate NK cell killing of tumor cells

NK inhibited by KIR

KIR blockade enhances NK killing and cytokine secretion

- Single agent activity being explored in ongoing AML Phase II (EffiKIR)
- Combination trials being tested in broad Phase I/II program
ANTI-KIR INDUCES KILLING OF PRIMARY AML BLASTS EX VIVO

*Ex vivo* killing of primary AML blasts by autologous NK cells from patient in remission
ANTI-KIR
ELIMINATION OF PRIMARY HUMAN AML IN NSG MICE

Romagne et al. Blood 2009
PHASE I TRIAL WITH HYBRIDOMA ANTI-KIR (IPH2101)

- Elderly AML patients in complete remission after induction and consolidation treatment - maintenance setting
- Phase I dose-escalation including 23 patients in first CR, and extension including 12 additional patients
- Doses ranged from 0.0003 to 3 mg/kg – Clear PK/PD relationship - Full KIR saturation at doses ≥1mg/kg
- Good tolerance with mild and transient adverse events. MTD not reached.

Vey et al., Blood Sept. 21 and ASH 2013 poster
PHASE I TRIAL WITH HYBRIDOMA ANTI-KIR (IPH2101) TRENDS IN CLINICAL OUTCOME RELATED TO KIR OCCUPANCY

- Suggested a correlation between full receptor occupancy and efficacy

- Clinical outcome (OS & PFS*) compared favorably to reports in comparable patient population

<table>
<thead>
<tr>
<th>Dose</th>
<th>N**</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 mg/kg</td>
<td>16</td>
<td>2.3</td>
<td>12.6</td>
</tr>
<tr>
<td>1-3 mg/kg</td>
<td>16</td>
<td>9.5</td>
<td>20.0</td>
</tr>
<tr>
<td>HR (95%CI)</td>
<td>16</td>
<td>0.515 (0.245; 1.081)</td>
<td>0.490 (0.219; 1.096)</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>0.075</td>
<td>0.076</td>
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</tbody>
</table>

* OS: Overall Survival, PFS: Progression Free Survival
**OS and PFS analyzed on 32 pts: 2 patients from extension excluded, one in CR2 and one for early relapse within 5-days and one in escalating part for absence of treatment

Vey et al., Blood 2012 and ASH 2013 poster
EFFIKIR PHASE II TRIAL
DOUBLE-BLIND PLACEBO-CONTROLLED RANDOMIZED TRIAL IN AML

- Target enrollment completed in July 2014 (150 patients)
  > N=50 per arm
- Treatment for 2 years
- Primary endpoint: Leukemia-Free Survival (Independent Review Committee)
- One active arm stopped in March 2015 upon DSMB recommendation
  > DSMB considered that treatment in the stopped arm could not be superior to placebo. There was no concern with tolerance

• Analysis of the primary endpoint, leukemia-free survival, is expected by early 2017

ClinicalTrials.gov Identifier: NCT01687387
COMBINING NK AND T CELL CHECKPOINT BLOCKERS
COMBINATIONS OF CHECKPOINT BLOCKERS CAN LEAD TO DEEPER RESPONSES AND IMPROVED SURVIVAL

1. Postow et al. NEJM 2015

- Combination of ipilimumab plus nivolumab approved in melanoma showed very deep and durable responses compared to either agent alone

Source: Citi Research
NK CELLS KILL TUMORS DIRECTLY, AND HELP T CELLS

Activation through KIR-blockade

Stimulation of T cells by NK cells

Activation through CTLA-4 or PD1 blockade
ANTI-KIR MOA SUGGESTS ATTRACTIVE BENEFIT-RISK PROFILE FAVORABLE FOR COMBINATION THERAPY

A. Tumor cell expressing activating ligand
   - No kill

B. Tumor cell expressing activating ligand
   - Kill

C. Normal cell not expressing activating ligand
   - No kill
SAFETY OF LIRILUMAB IN COMBINATION WITH T CELL CHECKPOINT INHIBITORS

- Two Phase I trials of lirilumab plus nivolumab or ipilimumab
- Conducted in patients with refractory solid tumors
  > Total of 181 patients enrolled in the two trials (incl. 159 for the lirilumab + nivolumab combo)
  > Lirilumab + nivolumab trial: lirilumab escalated from 0.1 to 3mg/kg Q4W in combo with nivolumab at 3mg/kg Q2W for up to 2 years
- No additional safety concerns were observed with lirilumab in combination with nivolumab or ipilimumab versus those observed with monotherapies
  > With the exception of an increase in low grade infusion-related reactions that were clinically manageable

- The combination of lirilumab and nivolumab in a phase I study of advanced solid tumors showed no added toxicity over nivolumab monotherapy

Segal et al., ESMO 2016 poster
**DEMOGRAPHICS OF PATIENTS WITH SCCHN TREATED WITH LIRILUMAB + NIVOLUMAB (CA223-001) OR NIVOLUMAB MONOTHERAPY (CHECKMATE 141)**

<table>
<thead>
<tr>
<th></th>
<th>Lirilumab + Nivolumab (n = 41)*</th>
<th>Nivolumab alone† (N = 240)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECOG PS, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>9 (22.0)</td>
<td>49 (20.4)</td>
</tr>
<tr>
<td>1</td>
<td>32 (78.0)</td>
<td>189 (78.8)</td>
</tr>
<tr>
<td>≥2</td>
<td>0</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td><strong>Tumor location, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>23 (56.1)</td>
<td>108 (45.0)</td>
</tr>
<tr>
<td>Pharynx and/or oropharynx</td>
<td>14 (34.1)</td>
<td>92 (38.3)</td>
</tr>
<tr>
<td>Larynx</td>
<td>3 (7.3)</td>
<td>34 (14.2)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2.4)</td>
<td>6 (2.5)</td>
</tr>
<tr>
<td><strong>Prior therapies, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>13 (31.7)</td>
<td>106 (44.2)</td>
</tr>
<tr>
<td>2</td>
<td>17 (41.5)</td>
<td>80 (33.3)</td>
</tr>
<tr>
<td>≥3</td>
<td>11 (26.8)</td>
<td>54 (22.5)</td>
</tr>
<tr>
<td><strong>HPV-positive oropharynx, n (%)‡</strong></td>
<td>8 (19.5)</td>
<td>63 (26.2)</td>
</tr>
</tbody>
</table>

*Of the 41 patients with SCCHN, 29 were evaluable for response. Majority of non-evaluable patients had not yet reached first on-study treatment assessment. 26 patients had post-baseline scans; 3 progressed prior to first scans.

** ECOG performance status was not reported in 1 patient in CheckMate 141.

† For CheckMate 141, HPV status according to p16 positivity.

## EFFICACY DATA IN CA223-001 AND CHECKMATE 141 IN EVALUABLE PATIENTS WITH SCCHN

<table>
<thead>
<tr>
<th></th>
<th>Lirilumab + Nivolumab</th>
<th>Nivolumab alone(^1)</th>
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</thead>
<tbody>
<tr>
<td><strong>ORR, n/N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>7/29 (24.1(^*))</td>
<td>32/240 (13.3)</td>
</tr>
<tr>
<td>Partial response</td>
<td>3 (10.3(^*))</td>
<td>6 (2.5)</td>
</tr>
<tr>
<td></td>
<td>4 (13.8(^*))</td>
<td>26 (10.8)</td>
</tr>
<tr>
<td><strong>DCR, n/N (%)</strong></td>
<td>15/29 (51.7)</td>
<td>NR</td>
</tr>
<tr>
<td><strong>ORR by PD-L1 expression, n/N (%)(^\dagger)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1%</td>
<td>0/9 (0)</td>
<td>9/73 (12.3)</td>
</tr>
<tr>
<td>≥1%</td>
<td>7/17 (41.2)</td>
<td>15/88 (17.0)</td>
</tr>
<tr>
<td>&gt;5%</td>
<td>6/11 (54.5)</td>
<td>12/54 (22.2)</td>
</tr>
<tr>
<td>≥50%</td>
<td>4/7 (57.1)</td>
<td>7/19 (36.8)</td>
</tr>
<tr>
<td><strong>Overall survival, % (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6 months</td>
<td>90(^\dagger)</td>
<td>55.6 (48.9, 61.8)</td>
</tr>
<tr>
<td>At 12 months</td>
<td>60(^$)</td>
<td>36.0 (28.5, 43.4)</td>
</tr>
</tbody>
</table>

\(^*\) Includes unconfirmed responses.

\(^\dagger\) PD-L1 expression was not determined in 3 patients; none of these patients were responders.

\(^\dagger\) Patients at risk, n = 15/41. \(^\$\) Patients at risk, n = 10/41.

PRELIMINARY MAXIMUM PERCENT REDUCTION IN TARGET LESIONS

IN EVALUABLE PATIENTS WITH SCCHN TREATED WITH LIRILUMAB + NIVOLUMAB (N = 26)*

Of the seven patients with a response, none were HPV-positive oropharyngeal patients.

*26 of 29 evaluable patients had a post-baseline assessment.

a Patient with a 37% reduction in target lesion classified as SD.
b Patient with a 100% reduction in target lesion classified as SD.
c Patient with a 30% reduction in target lesion classified as PD.
67-YEAR-OLD MALE PATIENT
WITH HPV-NEGATIVE SCCHN OF LARYNX

19 JUN 2014: 36 mm

2 SEP 2014: 25 mm
4 doses of nivolumab
+ 2 doses of lirilumab

6 JAN 2015: 0 mm
12 doses of nivolumab
+ 6 doses of lirilumab

Overall tumor burden:
45% decrease by RECIST

Overall tumor burden:
100% decrease of target lesions*

* Patient developed new lesions after 2nd cycle but continued in trial with resolution of target lesions
The median DOR was not reached

*26 of 29 evaluable patients had a post-baseline assessment.

a Patient with a 37% reduction in target lesion classified as SD.

b Patient with a 100% reduction in target lesion classified as SD.

c Patient with a 30% reduction in target lesion classified as PD.
LIRILUMAB + NIVOLUMAB IN SCCHN
CONCLUSIONS FROM INTERIM ANALYSIS OF CA223-001

• This is the first report of efficacy with the anti-KIR agent lirilumab in combination with nivolumab
• Potential for a differentiated profile in this patient population with enhanced clinical activity, particularly in inflamed tumors and with deep and durable responses observed in some patients
• The combination of lirilumab and nivolumab achieved an **ORR of 24% in 29 evaluable patients**
  > 41% in patients with inflamed tumors (>1% PD-L1 expression)
• Encouraging early overall survival data
• No added toxicity over nivolumab monotherapy observed
• Further evaluation of the safety and efficacy of lirilumab + nivolumab is ongoing in a broad exploratory program
• **Offers the potential for a new generation of IO/IO combinations**
**EXPLORATORY CLINICAL PROGRAM WITH LIRILUMAB**

- Broad Phase I and Phase II clinical trial program testing multiple indications and settings:

<table>
<thead>
<tr>
<th>Strategic approach</th>
<th>Mechanism of action</th>
</tr>
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<tbody>
<tr>
<td>Single-agent</td>
<td>NK cell checkpoint blockade</td>
</tr>
<tr>
<td>Combination with nivolumab</td>
<td>Combined NK and T cell checkpoint blockade</td>
</tr>
<tr>
<td>Combination with elotuzumab</td>
<td>ADCC enhancement</td>
</tr>
<tr>
<td>Combination with rituximab</td>
<td>ADCC enhancement</td>
</tr>
<tr>
<td>Combination with 5-azacytidine</td>
<td>Immune sensitization by chemotherapy</td>
</tr>
</tbody>
</table>

*As of Oct 2016, a total of 411 patients received lirilumab as part of this development program*
MONALIZUMAB (IPH2201), FIRST-IN-CLASS ANTI-NKG2A MAB CO-DEVELOPMENT AND COMMERCIALIZATION AGREEMENT WITH ASTRAZENECA
DISTINCT SUBSETS OF NK CELLS EXPRESS KIR OR NKG2A (OR BOTH)

Blood NK cells from four healthy donors (one in each panel) stained for KIR and NKG2A

Innate Pharma
NKG2A IS EXPRESSED ON TUMOR INFILTRATING LYMPHOCYTES

Upregulation of NKG2A on NK cells inside tumors

NKG2A on tumor infiltrating CD8⁺ T cells

Lung carcinoma

Cervical cancer

Blood NK (HC)  Intratumoral NK  Blood T cell  Intratumoral T cell

From L to R: Platonova et al. 2011, Sheu et al. 2005
MONALIZUMAB IS A FIRST-IN-CLASS NKG2A CHECKPOINT BLOCKER
MECHANISM OF ACTION

- NKG2A is an inhibitory receptor on tumor infiltrating CD8 T cell and NK cells
- Prevents interaction with HLA-E molecules to potentiate NK cells and CD8 T cells anti-tumor activity

NK cell and T cell inhibition by NKG2A

Activation by NKG2A blockade
MANY TUMORS OVEREXPRESS HLA-E, SUGGESTING A MAJOR MECHANISM OF IMMUNE EVASION

- HLA-E upregulated on a wide variety of tumor types:
  > H&N, Ovarian, Endometrium, Colorectal, Cervix, Lung, Oesophagus, CLL
- Restricted expression on normal tissues
- Clinical development plan informed by expression of HLA-E
HLA-E EXPRESSION MAY CONFER POOR PROGNOSIS

The example of lung adenocarcinoma:

<table>
<thead>
<tr>
<th>HLA-E (number, %)</th>
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</thead>
<tbody>
<tr>
<td>Low</td>
<td>55</td>
<td>(28 %)</td>
</tr>
<tr>
<td>High</td>
<td>142</td>
<td>(72 %)</td>
</tr>
</tbody>
</table>

Van der Burg et al Oncotarget 2015
MONALIZUMAB TARGETS NKG2A CHECKPOINT ON NK CELLS AND CD8 T CELLS

• NKG2A is an inhibitory receptor on tumor infiltrating CD8 T cells and NK cells
• NKG2A recognize HLA-E in humans and Qa-1 in mice

NK cell and T cell inhibition by NKG2A

Activation by NKG2A blockade
QA-1^b is induced on A20 cells *in vitro* by IFN-γ and *in vivo* after engraftment in mice.

Qa1 and PD-L1 expression also upregulated on tumor-infiltrating macrophages and monocytes.
Mice treated with indicated mAbs (200 µg, ip, 3 times every 3-4 days) were sacrificed on days 21 or 28 after tumor engraftment. CD8+ T cells were characterized by flow cytometry. Means +/- SD of % NKG2A+ PD-1+ CD8+ among CD8+ T cells. P<0.005 (**), P<0.0005 (****). N=3-6. % NKG2A+ NK cells among NK cells were not modified by anti-PD-1 treatment (data not shown).
COMBINING NK AND T CELL CHECKPOINT INHIBITORS
PRECLINICAL DEMONSTRATION WITH ANTI-NKG2A AND ANTI-PD-1

NKG2A blockade enhances the anti-tumor efficacy of PD-1/PD-L1 inhibitors

P<0.05 (*), P<0.005 (**), P<0.0005 (**).

*Sola et al., AACR 2016 poster*
### CLINICAL DEVELOPMENT OF MONALIZUMAB

<table>
<thead>
<tr>
<th>Exploratory clinical program ongoing (Phase I and Phase I/II)</th>
<th>Trials conducted in US and Europe will enroll up to 480 patients</th>
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</thead>
<tbody>
<tr>
<td>&gt; Selected indications informed by expression of HLA-E</td>
<td></td>
</tr>
<tr>
<td>&gt; Monalizumab tested as single agent (gynecological malignancies and hematological cancer)</td>
<td></td>
</tr>
<tr>
<td>&gt; Several combinations, including with anti-PDL1 durvalumab (solid tumors), ibrutinib (chronic lymphocytic leukemia) and cetuximab (head &amp; neck)</td>
<td></td>
</tr>
</tbody>
</table>

**Preliminary safety data of monalizumab as a single agent to be presented at ENA symposium 2016**

- Safety and first activity data for the dose-ranging part of the Phase I/II trial in patients with gynecological malignancies - EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics 2016 congress (29 November – 2 December, Munich, Germany)
INNATE PHARMA’S PIPELINE
TARGETING NK CELL CHECKPOINTS IN IMMUNO-ONCOLOGY

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- Monalizumab, anti-NKG2A
- NKp46-bispecific NK cell engagers
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