Redefining Allogeneic CAR Ts Using a Non-Gene Edited Approach

June 11, 2021
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<table>
<thead>
<tr>
<th>Topic</th>
<th>Discussant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Welcome &amp; Introductions</td>
<td>Filippo Petti</td>
</tr>
<tr>
<td></td>
<td>Chief Executive Officer</td>
</tr>
<tr>
<td>shRNA and CYAD-211 Overview</td>
<td>David Gilham, Ph.D.</td>
</tr>
<tr>
<td></td>
<td>Chief Scientific Officer</td>
</tr>
<tr>
<td>IMMUNICY-1 Phase 1 Trial – Preliminary Data</td>
<td>Sébastien Anguille, M.D.</td>
</tr>
<tr>
<td></td>
<td>University of Antwerp</td>
</tr>
<tr>
<td>Final Remarks</td>
<td>Charles Morris, M.D.</td>
</tr>
<tr>
<td></td>
<td>Chief Medical Officer</td>
</tr>
<tr>
<td>Q&amp;A</td>
<td>All</td>
</tr>
</tbody>
</table>
David Gilham, Ph.D.
Chief Scientific Officer

shRNA and CYAD-211 Overview
shRNA – Non-gene Editing Technology to Engineer Allogeneic CAR Ts

- Short hairpin RNA (shRNA) interferes with the expression of the T Cell Receptor (TCR) through targeting of the CD3ζ subunit.
Background on CYAD-211

- CYAD-211 is our first allogeneic CAR T candidate using shRNA technology utilizing our All-in-One vector approach
- CYAD-211 co-expresses:
  - CAR – BCMA specific engager
  - Allogeneic technology – single shRNA targeting CD3ζ component of TCR complex
  - Selection marker – truncated cell surface CD34 tag allows for positive cell enrichment during manufacturing

BCMA: B-cell maturation antigen; r/r MM: relapsed/refractory multiple myeloma.
Anti-BCMA CAR T cells with shRNA targeting CD3ζ component exhibited no signs of TCR activation with anti-tumor activity in preclinical models.

No demonstrable evidence of GvHD when CYAD-211 was infused in sub-lethally irradiated NSG mice, the gold standard preclinical model of GvHD, confirming efficient inhibition of alloreactivity.

**TCR Knock Down**

**Anti-Tumor Activity**

**Graft-versus-Host Disease**

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BCMA: B-cell maturation antigen; GvHD: Graft-versus-Host Disease; shRNA: short hairpin RNA.
shRNA Knocks Down TCR Expression to Undetectable Levels

Clinical-grade CYAD-211

- CYAD-211 cell bank generated through a single production run using a proportion of a single healthy donor apheresis
- Efficient knock down of cell surface TCR expression to undetectable levels was confirmed in the final CAR T-cell product candidate
shRNA as a Novel Allogeneic Technology for CAR T

*Keys to establishing proof-of-concept*

- No evidence of GvHD
- Initial clinical activity
- Cell engraftment
Sébastien Anguille, M.D.
University of Antwerp

IMMUNICY-1 Phase 1 Trial
– Preliminary Data
Open-label, Phase 1 dose-escalation trial in r/r multiple myeloma patients

Study Design

• Primary objective:
  • Safety and identification of recommended dose of CYAD-211
• Secondary objective:
  • Clinical anti-tumor activity and CYAD-211 cell expansion, persistence and trafficking
• Dose Escalation:
  • $30 \times 10^6$, $100 \times 10^6$ and $300 \times 10^6$ per infusion
• Preconditioning chemotherapy:
  • Cyclophosphamide: $300 \text{ mg/m}^2 \times 3 \text{ days}$
  • Fludarabine: $30 \text{ mg/m}^2 \times 3 \text{ days}$

Treatment Schedule

Eligibility Criteria

• At least two prior MM treatment regimens
• At least 1 complete cycle of treatment
• At least 1 response to a prior treatment regimen
• Measurable disease as per the IMWG Response Criteria
Patient Demographics and Clinical Characteristics

Patient Background

- Six patients enrolled across first two dose levels
- Three of six patients showed high-risk cytogenetics according to mSMART
- Four of six patients were refractory to last line of therapy
- Heavily pre-treated patients:
  - Median prior lines of therapy: four
  - Five of six patients exposed to all three major MM drug classes:
    - Immunomodulatory drugs (IMiDs), proteasome inhibitors and CD38-directed therapies
CYAD-211 – Preliminary Data Show Favorable Tolerability Profile

- No DLTs, no GvHD and no CAR-T-cell-related encephalopathy syndrome (CRES)
- One cytokine release syndrome (CRS) Grade 1 (fever) reported at dose level 1
- CRS onset was at the time of the first PR onset in patient #01
- One patient experienced an anemia adverse event (Grade 3) and neutropenia (Grade 4) possibly related to CYAD-211

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<th>AE of interest</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
<th>All Grades</th>
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<td>AE related to CYAD-211</td>
<td>5 (83%)</td>
<td>2 (33%)</td>
<td>1 (17%)</td>
<td>1 (17%)</td>
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<td>5 (83%)</td>
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<tr>
<td>CRS ¹</td>
<td>1 (17%)</td>
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<td>GvHD</td>
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<td>Infection ²</td>
<td>1 (17%)</td>
<td>1 (17%)</td>
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<td>-</td>
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<td>2 (33%)</td>
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<td>Infusion reaction to CYAD-211</td>
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</table>

2. Including bacterial, viral and fungal infections.

AE: Adverse event; GvHD: Graft versus Host Disease; PR: Partial response.
Data from uncleaned database (May 24, 2021).
CYAD-211 – Encouraging Initial Clinical Activity in Allogeneic Setting

Duration of Best Response to Treatment

- Two patients achieved partial response (PR)
- Three additional patients presented with stable disease (SD)

Patient bar stopped at the first documented progression of the disease or * when the patient discontinued follow-up on study prior to disease progression.

Data from uncleaned database (May 24, 2021).

PD: Progressive disease; MR: Marginal response
Positive Cell Kinetic Data

**CYAD-211 cell levels detected by PCR-based methods in all patients**

**Peripheral Blood Lymphocyte Count**
**CYAD-211 Cell Engraftment**

- Engraftment was seen in all three patients at dose level 2 at a similar magnitude.
- Duration and depth of lymphodepletion was variable and may explain differences in engraftment for dose level 1.
  - Patient #03 showed a surprisingly high level of engraftment compared to other dose level 1 patients.
IMMUNICY-1 Preliminary Results – Summary

- Favorable tolerability profile for CYAD-211 was observed at the first two dose-levels (30x10^6 and 100x10^6) across six patients enrolled.
- Two objective responses in conjunction with the current levels of cell engraftment of CYAD-211 are encouraging at these initial dose levels.
- Observed levels of systemic engraftment of CYAD-211 cells with no evidence of GvHD at low cell doses following standard preconditioning are encouraging.
Final Remarks
Advantages of Non-gene Edited Allogeneic CAR Ts using shRNA

Not all allogeneic CAR Ts are created equal

- Less potential tolerability issues due to no genome modification
- Level of gene knockdown can be titrated
- Ability to knockdown multiple targets simultaneously
- All-in-One vector approach (single vector for all elements)
- Minimized cell manipulation
- Shorter manufacturing process

Not all allogeneic CAR Ts are created equal
Even with relatively modest doses of lymphodepleting chemotherapy, there is evidence of a dose dependent increase in cell engraftment.

Engraftment of shRNA-based allogeneic CAR Ts could offer potential key differentiation to cells developed using alternative technologies.
shRNA as a Novel Allogeneic Technology for CAR T

*Keys to establishing proof-of-concept after dose level 1 and 2*

- ✔ No evidence of GvHD
- ✔ Initial clinical activity
- ✔ Cell engraftment
Next Steps for CYAD-211 IMMUNICY-1 Trial

- Enrollment in dose level 3 (300x10^6 cells per infusion) ongoing
- Additional data from the dose escalation trial are expected during second half 2021
• Safety data, clinical activity and cell kinetic data from IMMUNICY-1 support further development of CYAD-211
• Preliminary data support shRNA as a novel allogeneic platform technology to develop future product candidates
• Additional next-generation shRNA-based preclinical allogeneic CAR T candidates currently under development
• shRNA potentially provides many benefits over gene editing technologies for the development of allogeneic CAR T candidates
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