Phase 1 Studies Assessing the Safety and Clinical Activity of Multiple Doses of a NKG2D-based CAR-T Therapy, CYAD-01, in Acute Myeloid Leukemia

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CYAD-01 BACKGROUND

- CYAD-01 consists of engineered T cells expressing a CAR based on the natural killer receptor 2, member D receptor (NKG2D), a transmembrane receptor expressed by natural killer cells and some T-cell subsets.
- NKG2D binds to ligands frequently expressed on various tumor types (2,3). MHC class I i.i.d and the NKG2D receptor (NKG2D) and B (MHC) and Unique long 16 binding proteins (ULBP) 1-6 ligands.
- Preclinically, CYAD-01 have anti-tumor effects beyond direct cancer cell killing (4). Targeting neovascularization CYAD-01 ligands, Targeting immunosuppressive cells such as regulatory T cells and myeloid-derived suppressor cells expressing NKG2D ligands, Recruiting and activating macrophages and myeloid cells within the tumor stroma, shifting to an immunostimulatory TME, and Inducing a long-term memory immune response specific towards tumor antigens.

STUDY DESIGN

- CYAD-01 consists of one solid tumor and one in hematologic malignancies i.e. AML/MDS and MM.
- Standalone therapy: No bridging therapy, no preconditioning.
- 3+3 design dose escalation with 3 dose-levels (DL) of CYAD-01 (3×10^8, 1×10^9, and 3×10^9 cells/injection).
- 3 doses of CYAD-01 every 2 weeks.
- Potential 3 additional doses of CYAD-01 at 1×10^9 cells/injection according the clinical status at first tumor assessment.

STATUS (hematologic arm)
- 14 patients have been enrolled at three different dose-levels in the hematologic arm: 6 in DL-1, 3 in DL-2 and 5 in DL-3.
- Out of the 8 r/r AML pts enrolled as of July 31, 2018, 7 were evaluable for clinical response (2 at DL-1, 3 at DL-2 and 2 at DL-3) with promising anti-tumor activity (ASH 2018 - presentation 902, session 616 - Dec 3, 2018).
- As of Nov 27, 2018, three patients received the CYAD-01 injection following the preconditioning regimen with concurrent 5-azacytidine (AZA) (75 mg/m²/d x 7 days) every 4 weeks.
- As of Feb 28, 2019, 1 patient achieved complete remission (CR) with incomplete marrow recovery (CRi; 1 in DL-1 and 1 in DL-3), for 1 month.
- 2 patients at DL-2 had disease stabilization with hematologic improvement and bone marrow blasts decrease: one patient for 3 months and with a decrease from 2% to 10% and the second patient for at least 4 months (ongoing) and with a decrease from 9.8% to 5.5%.
- All responding pts achieved response by day 29 (i.e. after 2 CYAD-01 administrations).
- The 3+3 design dose escalation with 3 dose-levels of CYAD-01 (1×10^7, 3×10^8, and 1×10^9 cells/injection).
- 5-azacytidine chemotherapy and also the epigenetic treatment could contribute to favor engraftment of CYAD-01 cells and increase target antigen expression while better controlling the disease progression of patients early in the treatment.

CONCLUSIONS

- CYAD-01 has shown promising early clinical activity in relapsed/refractory AML with aggressive disease (4) with three responses observed.
- The safety profile of CYAD-01 as stand-alone treatment is favorable. As of Nov 27, 2018, the addition of CyFlu prior to CYAD-01 injection, while still early, does not increase the related AE rates at 12th injection.
- In terms of translational research, the THINK trial demonstrated expansion of peripheral CYAD-01 cells and cytokine release following CYAD-01 injections.
- Based on the data obtained with a CyFlu preconditioning in solid tumor indications (not shown here), cell kinetics data in the DEPLETHINK and EPITHINK study are expected to show increased expansion and persistence of the CYAD-01, potentially leading to higher clinical benefits rate. Clinical evaluation with schedule optimization w/o preconditioning is also currently tested.

TABLE 1: Related Adverse Events in the hematologic arm of THINK

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Prefered Term</th>
<th>Total pts with at least</th>
<th>N=6 (15 injections)</th>
<th>N=3 (12 injections)</th>
<th>N=5 (11 injections)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td></td>
<td>3 (50.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Weight increased</td>
<td></td>
<td>1 (16.7)</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Hypothermia</td>
<td></td>
<td>1 (16.7)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td>1 (16.7)</td>
<td>-</td>
<td>-</td>
<td>-</td>
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