Results from the completed dose escalation of the hematological arm of the phase I THINK study evaluating multiple infusions of NKG2D-based CAR T-cells as standalone therapy in relapsed/refractory acute myeloid leukemia and myelodysplastic syndrome patients

Background

The rapid approval of two anti-CD19 chimeric antigen receptor (CAR) T-cell therapies and advanced development of anti-BCMA CAR therapies demonstrate the potential of the approach in other diseases including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). However, targeting with a similar profile for CAR T-cell therapy in other diseases including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) lacks clinical data.

CYAD-01 is an autologous CAR T-cell therapy engineered with a multi-complex, second-generation NKG2D CAR comprising the full-length human natural killer cell group 2D (NKG2D) receptor fused to the intracellular domain of CD3ζ.

The NKG2D receptor targets β7 ligands (MHC class I chain related A [MICA] and B [MICB] and unique long 16 binding proteins (ULBP) 1-6 ligands) found at high frequency across a range of malignancies. Interestingly, non-malignant cells within the tumour microenvironment (myeloid-derived suppressor cells, regulatory T-cells and neo-endothelial cells) also express NKG2D ligands which led in preclinical models to the induction by CYAD-01 of a broader anti-tumor response beyond direct cancer cell killing.

The THINK study (NCT03101461) evaluates multiple administrations of CYAD-01 in r/r AML, MDS and multiple myeloma (MM) patients without any prior non-myeloablative preconditioning or bridging therapy.

The study design:
- Dose escalation segment with a Fibonacci 3+3 design evaluating (i) three dose levels (DL) of CYAD-01: 3x10⁸ (DL1), 3x10⁹ (DL2), and 3x10⁹ (DL3) cells per infusion, and (ii) two administration schedules for the 1st cycle of CYAD-01 infusions: every two weeks (biweekly schedule) or weekly (dose dense schedule). The dose dense schedule evaluates only the 3x10⁹ (DL2) and 3x10⁹ (DL3) cells per infusion.
- Expansion segment with the selected dose and schedule.
- Additional consecutive cycles of treatment if infusions were not evaluable in the absence of progression at the end of the first cycle (3x10⁹ or 3x10⁹ cells infusions).

Primary endpoint of the dose escalation segment is the occurrence of dose-limiting toxicity (DLT) during the CYAD-01 treatment phase. Patients who have not completed their first cycle of CYAD-01 administrations for other reasons than DLT should be replaced. Key secondary endpoints include additional safety parameters, objective responses, duration of responses, and CAR T-cell kinetics.

Study Status

25 patients have been enrolled so far in the dose escalation segment (ongoing).

Safety analysis is performed for the total treated patient population who received at least one CYAD-01 infusion including those 9 MM patients enrolled at the DL-1 biweekly schedule. Clinical activity and cell engraftment are assessed for the 22 r/r AML/MDS patients.

Table 1: Patient characteristics

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Patient count</th>
<th>CD3ζ MFI</th>
<th>CD3ζ viability %</th>
<th>CD3ζ expression %</th>
</tr>
</thead>
<tbody>
<tr>
<td>DL1</td>
<td>3x10⁸</td>
<td>2794.9</td>
<td>89.5</td>
<td>81.9</td>
</tr>
<tr>
<td>DL2</td>
<td>3x10⁹</td>
<td>2794.9</td>
<td>89.5</td>
<td>81.9</td>
</tr>
<tr>
<td>DL3</td>
<td>3x10⁹</td>
<td>2794.9</td>
<td>89.5</td>
<td>81.9</td>
</tr>
</tbody>
</table>

Table 2: Incidence of treatment-related adverse events (AEs) reported at least once as ≥Grade 3

<table>
<thead>
<tr>
<th>AEs</th>
<th>DL1 (3x10⁸)</th>
<th>DL2 (3x10⁹)</th>
<th>DL3 (3x10⁹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>11/25 (44%)</td>
<td>13/25 (52%)</td>
<td>14/25 (56%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3/25 (12%)</td>
<td>4/25 (16%)</td>
<td>5/25 (20%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2/25 (8%)</td>
<td>3/25 (12%)</td>
<td>3/25 (12%)</td>
</tr>
</tbody>
</table>

Figure 1: Time to engraftment and duration of treatment in AML/MDS patients

Figure 2: Best change in BM blast count from baseline in AML/MDS patients (%)

Figure 3: CYAD-01 kinetics in the peripheral blood

Main Results

- Patient demographics and tumor characteristics are summarized in Table 1.

The clinical activity data obtained recently with the dose dense schedule cohorts did not demonstrate an improvement of the clinical outcome. However, it is important to outline that these last enrolled pts presented with greater BM blasts infiltration and apparent more residual disease; DLT: dose-limiting toxicity; ELN: European LeukemiaNet; LTFU: lost to follow-up; mCR: marrow CR; m: month; ne: non-evaluable; PD: progressive disease; PR: partial remission; R-IPSS: Revised International Prognostic Scoring System; SD: stable disease

CONCLUSIONS AND PERSPECTIVES

The current results support a good safety profile of a multiple dose schedule with CYAD-01 without prior preconditioning chemotherapy in r/r AML/MDS patients.

- The anti-leukemic activity, although mostly of short durability, is promising in such refractory patient population. Even if the overall sample size of this Phase I study is small, the clinical activity does not seem to be correlated to the dose-levels and is predominantly observed in patients with High-Risk-IPSS advanced disease.

- The clinical activity data obtained recently with the dose dense schedule cohorts did not demonstrate an improvement of the clinical outcome. However, it is important to outline that these last enrolled pts presented with greater BM blasts infiltration and apparent more profound pancytopenic status at baseline than the first enrolled patients who received the biweekly schedule. Whether this blunted CYAD-01 activity remains open to question.

Further recruitment into the THINK trial will use the OptimaAb manufacturing process.

Acknowledgements & Disclaimer

This study was funded and sponsored by CYAD SAS (Paris, France) and directed by the Principal Investigator at the INRAE (INRAE, CNRS, University of Montpellier, France) and the Principal Co-investigator at the Erasme University Hospital (Brussels, Belgium).

The views expressed are those of the authors and do not necessarily those of the organizations named herein.