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

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BACKGROUND

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

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 group 2D (NKG2D) receptor fused to the intracellular domain of CD3ζ. The NKG2D receptor targets ligands (LGs) including MHC class I chain related proteins A (MICA) and B (MICB) and unique long 16 binding proteins (ULBP) I–6 LGs found at high frequency across a range of malignancies. Interestingly, non-malignant cells within the tumor 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 open-label Phase I THINK study (NCT03101641) 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 1:1.5 design evaluating three dose levels (DL3: 3x10^8 cells/inf; DL2: 3x10^9 cells/inf), and 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 3x10^8 (DL-2) and 3x10^9 (DL-3) cells-per-infusion.
- Expansion segment with the selected dose and schedule.
- Biweekly or dose dense cycle of treatment if infusions are two weeks apart in the absence of progression at the end of the first cycle (1x10^9 or 3x10^9 cells-per-infusion).
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- Biweekly schedule DL-1: 3.10^8 cells/inf.
- Biweekly schedule DL-2: 3.10^9 cells/inf.
- Biweekly schedule DL-3: 3.10^9 cells/inf.
- Dose dense schedule DL-1: 3.10^9 cells/inf.
- Dose dense schedule DL-2: 3.10^9 cells/inf.
- Dose dense schedule DL-3: 3.10^9 cells/inf.
- 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.

TABLES & FIGURES

Table 1: Patient characteristics

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

Figure 1: Time to response 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

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 rate, 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 a high risk score (Antileukemic activity rate of 24% in adverse ELN2017 (AML)/very high R-IPSS (MDS) risk stratification categories). 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.

Given the tolerability and short-term clinical activity of CYAD-01, efforts have been made to optimize the manufacturing process (“OptimAb”) under the THINK study (poster 3844), to enrich for early memory phenotype CAR T-cells that showed enhanced anti-tumor activity in preclinical models (poster 3844).

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

ACKNOWLEDGEMENTS & DISCLAIMER

Clinical trials patients are live persons,全过程，临床试验的参与者。

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