The rapid approval of two anti-CD19 chimeric antigen receptor (CAR) T-cell therapies and advanced development of anti-BCMA CAR T-cell therapy demonstrates 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) are lacking.

CYAD-01 is an autologous CAR T-cell therapy engineered with a multi-chain, second-generation NKGD2 CAR comprising the full-length human natural killer group 2D (NKGD2) receptor fused to the intracellular domain of CD3ζ.

The NKGD2 receptor targets ligands (HMHC class I chain related proteins A (HICA) and B (HICB) 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 tumor microenvironment (myeloid-derived suppressor cells, regulatory T-cells and neo-endothelial cells) also express NKGD2 ligands which led in preclinical models to the induction by CYAD-01 of a broader anti-tumor response beyond direct cancer cell killing.

CYAD-01 is being evaluated in relapsed/refractory (r/r) AML/MDS patients, with the objective to define whether the optimal CYAD-01 treatment is with or without pre-conditioning chemotherapy (DEPLETHINK). Study details are discussed or without any pre-treatment (see THINK study, poster 3823).

DEPLETHINK STUDY

The open-label Phase I/II DEPLETHINK Study (NCT03665250) evaluates a single infusion of the autologous CYAD-01 administered after a non-myeloablative preconditioning chemotherapy in r/r AML or MDS patients.

The preconditioning chemotherapy consists of 500 mg/m² cyclophosphamide and 50 mg/m² fludarabine daily for 5 days (CyFlu). This preconditioning chemotherapy should (i) favor the proliferation and expansion of CAR T-cells and (ii) increase the NKGD2 ligand expression in tumor tissues targeted by CYAD-01.

Dose escalation segment with a Fibonacci 3-1-2: Three dose levels (DL) of CYAD-01: 1x10⁸, 3x10⁸ and 1x10⁹ cells per infusion administered as a single infusion after the preconditioning chemotherapy.

The first DL of CYAD-01 was evaluated at low dose levels (1, 3x10⁸) for safety reasons on first-time-in-human infusion of an AML CAR T-cell post chemotherapy.

The first DL of CYAD-01 was evaluated at two intervals between preconditioning and CYAD-01 infusion (48h preconditioning treatment administered 7 days (T7) or 3 days (T3) before CYAD-01 infusion) to evaluate any potential modulation of the CYAD-01 cell-engagement.

Potential CYAD-01 consolidation cycle of 5 infusions every two weeks without prior preconditioning chemotherapy in the absence of progressive disease (PD) one month after the first CYAD-01 infusion.

Primary endpoint of the dose escalation segment is the occurrence of dose-limiting toxicity (DLT) during the CYAD-01 treatment phase. Key secondary endpoints include additional safety parameters, CYAD-01 cell kinetics, objective responses and duration of responses.

A potential Phase II segment is planned according to specific fidelity analysis at the end of the dose escalation segment.

With respect to the CYAD-01 product, the current manufacturing process (mAb process), used to date in the DEPLETHINK study, tends to produce more differentiated T-cells that are highly active in killing tumor activity as compared to the currently used mAb-manufactured CYAD-01 at the same dose of cells (Figure 1).

Celyad has developed a new process named ‘OptimAb’, which generates a higher frequency of less differentiated CYAD-01 T-cells as compared to previous process (Figures 2 and 3). The ‘OptimAb’ manufacturing process provides a higher differentiation of the CAR T-cells (CD62L expression) and interferon-gamma upon challenge with tumor cells.

In a preclinical model, the OptimAb-manufactured CYAD-01 showed much improved long-term anti-tumor activity as compared to the currently used mAb-manufactured CYAD-01 at the same dose of cells (Figure 4).

OPTIMIZED MANUFACTURING PROCESS

Study Status (Table 1)

- 9 patients have been enrolled so far in the two first DLs of the dose escalation segment of this Phase I/II study with the current mAb process.
- The recruitment has been re-initiated at DL-2 with the OptimAb-manufactured CYAD-01 for safety and cell kinetics comparability reasons (ongoing, data not shown).
- An encouraging safety profile was observed (Table 2) for all at CYAD-01 infusions post CyFlu preconditioning chemotherapy. To note, at the 1st CYAD-01 infusion of the consolidation cycle (3x10⁸ cells per infusion) in one of the patients at Grade 0/1 cytokine release syndrome (CRS) and a G3 CRS T-cell related neurological syndrome (CNS) and 1 patient at DL-2 experienced a G3 CRS. All patients recovered with treatment including tocilizumab.
- No objective response has been observed at the first two DLs but 3/9 patients did not progress one month after the first CYAD-01 infusion and were eligible for the consolidation cycle.
- For the first 2 DLs evaluated with the mAb process, the CYAD-01 cell engagement is dose-dependent (Figure 1), and the addition of the CyFlu as preconditioning induces a better time-averaged engraftment compared to the CYAD-01 injected without preconditioning (Figure 1) and THINK poster 3823.

CONCLUSIONS

To date, the results demonstrate the safety of 1x10⁸ and 3x10⁸ mAb-manufactured CYAD-01 cells infusion administered after cyclophosphamide/fludarabine preconditioning chemotherapy.

The pre-conditioning regimen increases the engraftment of the CYAD-01 cells as compared to cells infused without preconditioning, and, for the first 2 DLs evaluated, the CYAD-01 cell engagement is dose-dependent.

In a preclinical model, CYAD-01 produced with an optimized manufacturing process (‘OptimAb’) showed an improved long-term anti-tumor activity at the same dose as compared to the currently used process.

The DEPLETHINK study has been reinitiated at DL-2 with the OptimAb-manufactured CYAD-01 product, which should help to increase the expansion of the cells and favor long-term anti-tumor activity.

In parallel, the OptimAb-manufactured CYAD-01 will be also evaluated without prior preconditioning therapy (‘OptimAb’ and a next-generation MGD2 CAR, ‘CYAD-01’, which includes features favoring the persistence of the CAR T cells in vivo, will be evaluated into the CYCLE-1 Phase I study (NCT04151096) post preconditioning chemotherapy (post 3823), both in the same patient population.