Updated results from Phase I trials assessing a NKG2D CAR T-cell approach in relapsed/refractory acute myeloid leukemia and myelodysplastic syndrome patients

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CD4-1 BACKGROUND

- CD4-1 cells are engineered T cells expressing a chimeric antigen receptor (CAR) based on the natural full-length human natural killer group 2D (NKG2D) receptor fused to the cytoplasmic domain of CD3ε.
- Ligand binding to CD4-1 triggers a primary signal via CD3ε and a secondary signal via the adaptor molecule DAP-10.
- CD4-1 binds to 8 ligands (MHC class I chain related proteins A (MICA) and B (MICB) and Unique long tendon binding proteins (ULBP) 1-4) ligands expressed by a large variety of malignancies, including acute myeloid leukemias (AML) and myelodysplastic syndromes (MDS) (1,2).
- Precisely, CD4-1 has anti-tumor effects beyond direct cancer cell killing by targeting also cells from the tumor microenvironment and neo-vascularized cells expressing NKG2D ligands, and boosting an adaptive anti-tumor immune response.

CD4-1 IN AML/MDS

- CD4-1 is currently evaluated in relapse/refractory (r/r) AML/MDS patients in a clinical development plan with the objective to define the optimal CD4-1 treatment with or without prior preconditioning chemotherapy.

- The THINK (NCT03161445) open-label Phase I study evaluates the safety and clinical activity of CD4-1 administered as a standalone therapy with a multiple infusion schedule in patients with different indications including r/r AML and MDS.

- No myeloablative preconditioning chemotherapy.
- No bridging therapy.

- 3 X design: dose escalation: 3 dose-levels (DL) of CD4-1 (3×10^9, 1×10^9 and 3×10^9 cells/infusion) for the 1st cycle of 3 CYAD-01 infusions Q2W.

- 2 DL of CD4-1 (1×10^9 and 3×10^9 cells/infusion) for the 1st cycle of 3 CYAD-01 infusions Q2W (dense schedule).

- Potential 2nd cycle of CYAD-01 infusions Q2W in absence of progressive disease (PD) at the end of the 1st cycle.

- Recruitment at 1×10^9 cell/infusion DL of the dense schedule is ongoing.

- The DEPLETHINK (NCT03166520) open-label Phase I study evaluates the safety and clinical activity of CD4-1 administered after a preconditioning regimen in r/r AML and MDS patients.

- 3 X design: dose escalation: 3 DL (1×10^4, 3×10^4, 1×10^5 and 1×10^5 cells/infusion).

- Preconditioning regimen (500 mg/m² cyclophosphamide and 30 mg/m² fludarabine daily for 3 days) prior to a single CD4-1 isolation.

- First DL at a safety low dose of CD4-1 (1×10^5 cells/infusion i.e. 1.5×10^6 cells/kg) and evaluated at 2 intervals between preconditioning and CD4-1 infusion (7-7 days interval, T3, 3 days) for safety precaution to mitigate for any potential increased toxicity due to the administration of the preconditioning chemotherapy.

- Potential 2nd X of 3 CYAD-01 infusions Q2W with preconditioning in case of no PD after 1st infusion.

- Recruitment in DL-2 ongoing (3×10^5 cells/infusion).

OVERALL RESULTS

- All together, results obtained to date in both Phase I studies demonstrate the safety of CD4-1 w/o or with a prior preconditioning chemotherapy in patients with r/r AML and MDS.

- Preliminary anti-leukemic activity, although mostly of short durability, observed in 46% of patients after multiple CYAD-01 infusions in the absence of preconditioning chemotherapy is highly promising in such refractory patient population.

- Data on an initial dose-level with a denser schedule of infusions showed a better CD4-1 cell engraftment. The THINK study is now recruiting at the dense schedule with 3×10^9 cells/infusion.

- These initial clinical and persistence data suggest a potential improvement of the clinical response durability could be obtained through an optimized infusion schedule or addition of a preconditioning regimen.

REFERENCES

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Main results

- Multiple infusions of CD4-1 without any prior conditioning chemotherapy showed:

- An encouraging safety and tolerability profile with a manageable (G1) 3/4 treatment-related adverse events (AEs).

- CRS occurred in 10 pts with only 2 G1 CRS and 1 G4 CRS, which resolved with tocilizumab treatment. No treatment-related neurotoxicity AEs.

- Encouraging preliminary anti-leukemic activity with 6/13 pts (46%) presenting relevant BM blasts decrease in r/r AML/MDS pts evaluated per protocol with 4 objective responses (CR,CRi,mCR).

- Most responses were of short durability. The dense schedule at 1×10^9 cells/infusion did not modify the overall tolerability safety profile.

- DEPLETHINK: single infusion of a safety low dose of CYAD-01 (≤1.5×10^9 cells post pre-conditioning chemotherapy showed:

- No G2/3 treatment-related AE.

- CRS G2 occurred in 5 pts (two G1 and 1 G2).

- 27% pts with SD post first CYAD-01 infusion at sub-therapeutic DLS were eligible for a consolidation cycle of 3 CYAD-01 infusions w/o preconditioning.

- Evaluation of higher dose-levels similar to those from the THINK study are ongoing.

- CD4-1 pharmacodynamics data:

- CYAD-1 is detected in peripheral blood after the first infusion at all dose levels.

- Persistence of cells after infusion with no prior pre-conditioning was not durable, in agreement with preclinical data.

- Better time-averaged engraftment area under the curve was observed with the dense schedule of infusions.

- Better time-averaged engraftment was observed after a single infusion of a low dose of CYAD-1 with a prior pre-conditioning, especially if the interval between the preconditioning regimen and CYAD-1 was short (3 days (TS) better than 7 days (TI)).