Results and perspectives from Phase I studies assessing the safety and clinical activity of multiple doses of a NKG2D-based CAR-T therapy, CYAD-01, in metastatic solid tumors

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**CHimeric antigen receptor (CAR) T-cell therapies** have yet to demonstrate positive results in the context of solid tumors likely because of the inability of classical CAR-Ts to infiltrate into the tumor (dense tumor stroma and bloodstream pH and low nutrient conditions) and overcome the hostile immune suppressive tumor microenvironment (TME).

**CYAD-01** consists of engineered T cells expressing a CAR based on the natural killer group 2 member D receptor (NKG2D), a transmembrane receptor expressed by natural killer cells and some T-cell subsets.

NKG2D binds to 8 ligands frequently expressed on various tumor types [1, 2]: MHC class I chain-related proteins A (MICA) and B (MICB) and of Long 16 binding proteins (ULBP) 1-6 ligands.

Precociously, CYAD-01 have anti-tumor effects beyond direct cancer cell killing [3]:
- Targeting revascularization expressing NKG2D 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,
- Inducing a long-term memory immune response specific towards tumor antigens.

**CYAD-01 DEVELOPMENT**

- **CYAD-01** is currently evaluated in hematologic and solid cancer indications in a comprehensive clinical development program (Figure 1). CYAD-01 showed promising early clinical activity in relapsed/refractory AML [4] and is also evaluated in solid tumor indications in different settings.

**FIGURE 1: CYAD-01 clinical development**

**MAIN RESULTS**

- **The THINK (NCT03018405) study** - solid tumor arm - aims at evaluating the safety and clinical activity of CYAD-01 therapy administered as a standalone therapy in patients with different relapsed/refractory solid tumor indications.
- **The THINK CyFlu cohort** (NCT03018405) aims at evaluating the safety and clinical activity of CYAD-01 therapy administered after a pre-conditioning regimen (cytosphosphamide and fludarabine) in patients with relapsed/refractory mCRC. This corresponds to the schedule used with classical CAR T-cell therapies and aims at providing a better CYAD-01 engrafment due to the lymphodepletion of host cells.
- **The SHRINK (NCT0311008) study** has been designed to address the challenges specific to solid tumors and related to the immunomodulation of the TME by evaluating CYAD-01 therapy concurrently administered with the FOLFOX standard of care (SoC) chemotherapy regimen in patients with mCRC. Concurrent administration of SoC aims at providing additional CYAD-01 activity due to the lymphodepletion induced by the FOLFOX and improving disease control prior to CYAD-01 infusion. The study is conducted in mCRC patients either with potentially resectable liver metastasis (meso-diagnostic setting) or with recurrent/progression disease at least one line of prior systemic therapy for metastatic disease.
- **CONCLUSIONS**
  - CYAD-01 has shown promising early clinical activity in relapsed/refractory AML [4].
  - In solid cancer indications, the safety profile of CYAD-01 as stand-alone treatment seems favorable. The addition of Cy/Flu or FOLFOX, while still early, does not seem to increase the related-AEs rate.
  - In terms of clinical activity, the THINK trial demonstrated encouraging disease stabilization in relapsed/refractory metastatic CRC and ovarian cancer patients. Some interesting preliminary correlation can be done between the clinical benefit and the expansion of peripheral CYAD-01 cells.
  - Cell kinetics data in the THINK CyFlu cohort are encouraging as we await clinical data to explore the correlation between clinical activity and cell expansion.
  - Early data in the neoadjuvant setting (SHRINK trial) with the 3 patients showing a pathological complete response is ongoing and will be further explored in the next dose levels.