Phase 1 Studies Assessing the Safety and Clinical Activity of Multiple Doses of a NKG2D-based CAR-T Therapy, CYAD-01, in Metastatic Colorectal Cancer

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CYAD-01 CAR T-cell Therapy

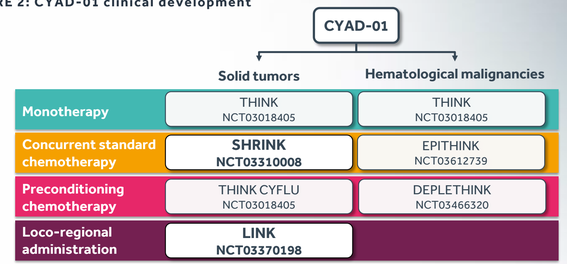
- **Chimeric antigen receptor** (CAR) T-cell therapies have yet to demonstrate positive results in the context of solid tumors likely because of the inability of classical CAR-Ts to infiltrate into the tumor (dense tumor bed and bulky stroma, hypoxic, low pH, and low nutrient conditions) and overcome 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 stress-inducible ligands** frequently expressed on various tumor types [1,2]: MHC class I chain–related proteins A (MICA) and B (MICB) and Unique long 16 binding proteins (ULBP) 1–6 ligands [see also poster 1179P].
  - Preclinical results: CYAD-01 may have anti-tumor effects **beyond direct cancer cell killing** [3] (**Figure 1**) by:
    - Targeting neovasculature expressing NKG2D ligands,
    - Cytotoxic killing of immunosuppressive cells within the tumor microenvironment (TME) such as regulatory T cells and myeloid-derived suppressor cells expressing NKG2D ligands,
    - Recruiting and activating macrophages and myeloid cells within the tumor stroma, causing a shift from an immunosuppressive to an immunostimulatory TME, and
    - Inducing a long-term memory immune response specific towards tumor antigens.

CYAD-01 Clinical development

- CYAD-01 is currently evaluated in the ongoing THINK study (NCT03018405) without preconditioning therapy in **both hematologic and solid cancer indications**, and demonstrated **encouraging signs of clinical stabilization** in refractory metastatic colorectal (mCRC). These preliminary results prompted us to design a clinical development plan evaluating CYAD-01 in multiple settings (**Figure 2**).

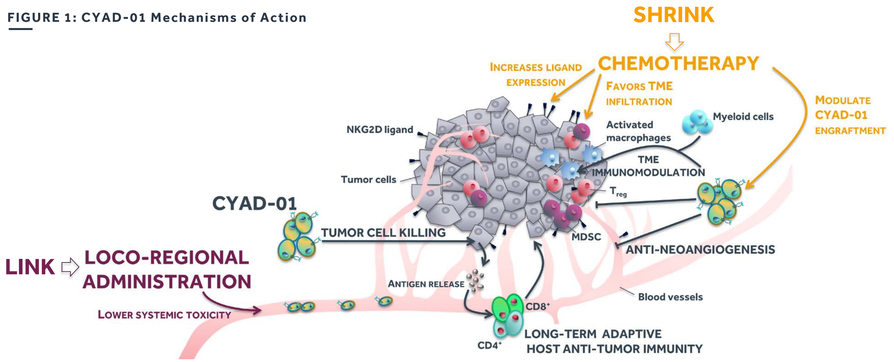
FIGURE 2: CYAD-01 clinical development



- The **LINK** (NCT03370198) and the **SHRINK** (NCT03310008) trials have been designed to address the challenges specific of solid tumors and related to the immunosuppressive TME and difficulty of CAR-T cells to access the site of metastases (**Figure 1**).

LINK & SHRINK Background and Study rationales

FIGURE 1: CYAD-01 Mechanisms of Action



LINK Study Rationale

- The **LINK** (**L**ocoregional **I**mmunotherapy with **NK**R-2, NCT03370198) study is an open-label, dose escalation, phase 1 clinical trial to assess the safety and clinical activity of multiple hepatic transarterial administrations of CYAD-01 in mCRC patients with unresectable liver metastases with the potential advantage of :
  - A lower systemic toxicity and higher and more persistent concentration of the infused cells on the TME compared to systemic administration,
  - Difference in blood supply between uninvolved liver parenchyma and metastases, and
  - Boosting of the adaptive immune response by CYAD-01 might control distant lesions thanks to a possible abscopal effect.

SHRINK Study Rationale

- The **SHRINK** (**S**tandard c**H**emotherapy **R**egimen and **I**mmunotherapy with **NK**R-2, NCT03310008) study is an open-label, phase 1 clinical trial designed to investigate the safety and activity of multiple CYAD-01 treatments i.v. administered concurrently to a standard-of-care FOLFOX chemotherapy treatment in mCRC disease with the aim to:
  - Favor infiltration into the immunosuppressive TME,
  - Provide an opportunity for the CYAD-01 cells to better engraft due to the lymphodepletion induced by the FOLFOX,
  - Increase the NKG2D ligand expression in tumor tissues targeted by CYAD-01, and
  - Improve the disease control due to the direct cytotoxic effect of chemotherapy administered prior to and concurrently with CYAD-01 infusion.

References
[1] Nausch N, Cerwenka A. *Oncogene* 2008;27:5944-58.
[2] Lanier L. *Cancer Immunol Res* 2015;3(6):575-82.
[3] Lonez C, et al. *BMJ Open* 2017;7:e017075.
See also our other posters (1178P and 1179P) for further information.

LINK Study Design & Status

- The **LINK** study consists of a dose escalation which assesses 3 dose levels of CYAD-01 (3×10^8, 1×10^9 and 3×10^9 cells/injection) according to a standard 3+3 design to determine the maximum tolerated dose (MTD) and the recommended dose level (RecD).
- Patients will receive 3 doses of CYAD-01 infused by hepatic transarterial administration at 2-week intervals.
- The patient must have a histologically proven adenocarcinoma of the colon or rectum with unresectable liver metastases and has:
  - Measurable hepatic metastases defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1,
  - Maximum 2 extra-hepatic metastatic organ localizations with at least 1 extra-hepatic metastasis measurable by RECIST version 1.1,
  - Received at least one prior chemotherapy line for metastatic disease and have developed resistance or intolerance to this treatment.

Study Status
- The first patient was recruited in Q1 – 2018.
- The estimated primary completion date is Q3 – 2019.

SHRINK Study Design & Status

- The **SHRINK** study consists of a dose escalation which assesses 3 dose levels of CYAD-01 (1×10^8, 3×10^8, and 1×10^9 cells/injection) according to a standard 3+3 design to determine the MTD and RecD, and a dose expansion to further evaluate safety and activity of CYAD-01 at the RecD in 21 additional patients.
- Patients will receive 6 cycles of FOLFOX every 2 weeks, and 3 doses of CYAD-01 every 2 weeks administered at specific times within the chemotherapy cycles.
- Patients must have either
  - A histologically proven colorectal adenocarcinoma with resectable liver metastases and
    - No evidence of extra-hepatic metastases, with the exception of completely resectable pulmonary metastases,
    - Measurable hepatic disease by RECIST version 1.1,
    - No previous chemotherapy for metastatic CRC,
    - Due to receive first-line metastatic chemotherapy regimen with FOLFOX as a neoadjuvant.
  - A confirmed metastatic unresectable colorectal adenocarcinoma and
    - A recurrent/progressing disease after at least one line of systemic therapy for metastatic disease,
    - Due to receive FOLFOX chemotherapy,
    - Measurable disease by RECIST version 1.1.

Study Status
- The first patient was recruited in Q1 – 2018.
- Dose-level 1 ($1x10^8$ cells/injection) is completed and experienced no serious adverse event.
- Feasibility and safety – no DLT to date.
- Patients are currently being enrolled for dose-level 2.
- The estimated primary completion date for the dose escalation is Q2 – 2019.