Celyad

CT134

A Phase 1 study assessing the safety and clinical activity of multiple hepatic transarterial administrations of an NKG2D-based CAR-T therapy, CYAD-01, in patients with unresectable liver metastases from colorectal cancer

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CYAD-01 CAR T-Cell Therapy

- CYAD-01 (previously named NKR-2) is an adoptive cell therapy consisting of engineered T cells expressing a chimeric antigen receptor (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 cancer cells [1,2]:
    - MHC class I chain–related proteins A (MICA) and B (MICB)
    - Unique long 16 binding proteins (ULBP) 1–6 ligands
  - The CYAD-01 CAR is composed of the full-length human NKG2D fused to the CD3ζ cytoplasmic signaling domain (**Figure 1**)
  - The surface adaptor molecule DNAX-activating protein of 10kDa (DAP-10), which is endogenously expressed on T cells, associates with and stabilizes CYAD-01 CAR expression
  - Ligand binding to CYAD-01 triggers a primary signal via CD3ζ and a secondary signal via DAP-10, resulting in efficient T-cell co-stimulation and cytotoxicity
- CYAD-01 showed promising results in multiple preclinical models and in the clinic [3, Poster CT134]
- Preclinical results indicate CYAD-01 may have anti-tumor effects beyond direct cancer cell killing [4]:
  - 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
  - Inducing a long-term memory immune response specific towards tumor antigens
- CYAD-01 may be an effective therapy for solid and hematological tumor types that express NKG2D ligands and is currently being investigated in comprehensive clinical program (**Figure 2**)

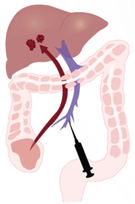
Colorectal Cancer (CRC)

1.4M new cases per year [5]

3rd most common cancer in ♂

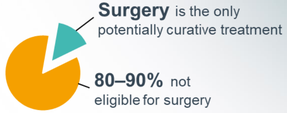
2nd most common cancer in ♀

100% express **≥1 NKG2D ligand** [6]



50% of patients develop metastases [7]

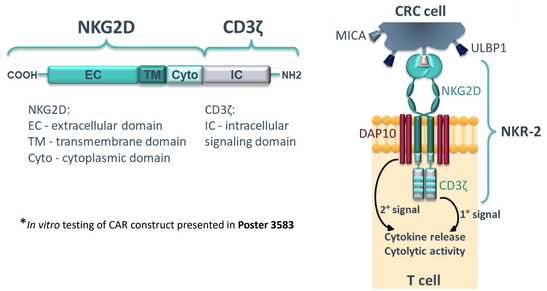
Liver is the most frequent site of metastasis



Intra-arterial delivery of therapy may enable clinical activity and minimize toxicity [8,9]

Figures and Tables

FIGURE 1: CYAD-01 CAR construct* and expression in engineered T cells



*_In vitro_ testing of CAR construct presented in **Poster 3583**

FIGURE 2: CYAD-01 clinical development

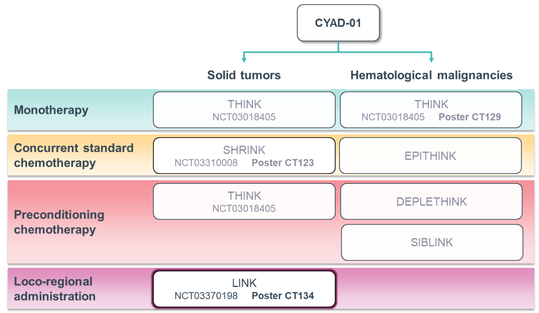


FIGURE 3: LINK treatment schedule

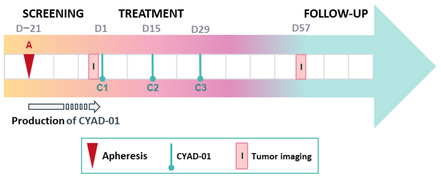


TABLE 1: LINK key eligibility criteria

Inclusion criteria	Exclusion criteria
• Histologically confirmed CRC with nonresectable hepatic metastases	• Extra-hepatic metastases, unless ≤2 asymptomatic lung and/or lymph node metastases
• Resistance or intolerance to 1 prior line of chemotherapy for metastatic disease	• Insufficient bone marrow reserve, hepatic or renal function
• Liver metastases measurable by RECIST v1.1	• ECOG performance status ≥2

ECOG, Eastern Cooperative Oncology Group; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1

TABLE 2: LINK study endpoints

	Endpoints
Primary	– Occurrence of dose-limiting toxicity
Secondary	– Clinical activity – Additional safety parameters
Correlative	– Kinetics of CYAD-01 in peripheral blood – CYAD-01 presence in hepatic metastases – Systemic cytokine levels post-CYAD-01 treatment

LINK Study Rationale

- CAR T cells targeting solid tumors face additional obstacles compared with those targeting hematological malignancies [10,11]:
  - Inaccessible, dense tumor bed and bulky stroma
  - Hypoxic, low pH, and low nutrient conditions
  - Immunosuppressive milieu due to the activation of inhibitory immune checkpoint pathways, the secretion of anti-inflammatory factors, and the presence of immune suppressor cells
- Delivery of CYAD-01 via the hepatic artery may enhance clinical activity while limiting systemic exposure and toxicity by:
  - Increasing homing of CYAD-01 to tumors, benefitting from the different blood supply to uninvolved liver parenchyma and to liver metastases
  - The release of tumor antigens via direct anti-cancer cytotoxicity may trigger the host immune system, boosting the adaptive immune response, thus potentially resulting in the control of any distant lesions (abscopal effect)
  - Allowing the administration of higher doses compared to systemic delivery

LINK Trial Design

- LINK (**L**ocoregional **I**mmunotherapy with **NK**R-2, NCT03370198) is an open-label, dose escalation, phase 1 clinical trial to assess the safety and clinical activity of CYAD-01 infused by hepatic transarterial administration in CRC patients with unresectable liver metastasis
  - Patients will receive 3 doses of CYAD-01 at 2-week intervals (**Figure 3**)
  - CYAD-01 will be assessed at 3 dose levels (3×10^8, 1×10^9, and 3×10^9 CYAD-01 cells per injection), according to a standard 3+3 design, to determine the maximum tolerated dose and the recommended phase 2 dose
- Key eligibility criteria are shown in **Table 1**
- Study endpoints are shown in **Table 2**

Assessments

- Tumor assessments will be performed by CT imaging or MRI at baseline and 4 weeks after the last dose of CYAD-01
- Tumors will be biopsied at baseline, 2 weeks post-CYAD-01 treatment, and at the time of hepatic metastasis resection, if applicable
- CYAD-01 and cytokines will be quantified in peripheral blood

Study Sites and Dates

- The first patient was recruited in January 2018
- Patients are currently being enrolled at the Institut Jules Bordet, Brussels, Belgium
- The estimated primary completion date is July 2019

References

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