Celyad

CT123

A Phase 1 study assessing the safety and clinical activity of multiple doses of an NKG2D-based CAR-T therapy, CYAD-01, administered concurrently with neoadjuvant FOLFOX treatment in patients with potentially resectable 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**)

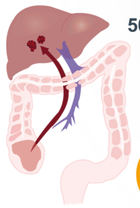
Colorectal Cancer (CRC)

1.4M new cases per year [5]

3rd most common cancer in ♂

2nd most common cancer in ♀

100% express ≥1 **NKG2D ligand** [3]



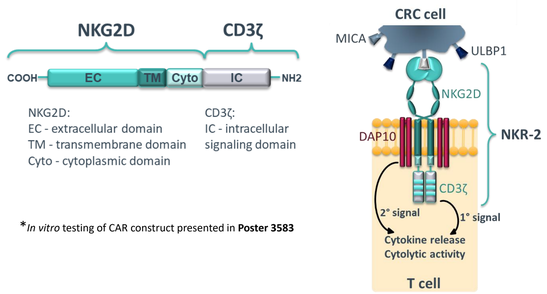
50% of patients develop metastases [6]

Liver is the most frequent site of metastasis

FOLFOX (**folinic acid + 5-FU + oxaliplatin**) neoadjuvant treatment before resection of liver metastases

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

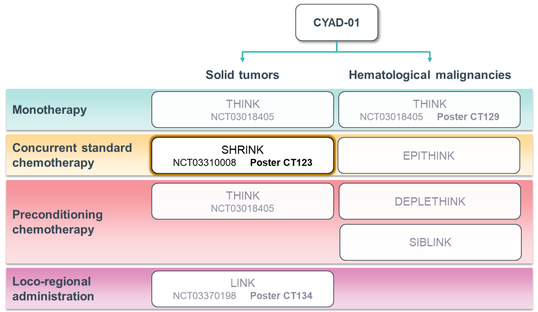


FIGURE 3: SHRINK treatment schedule

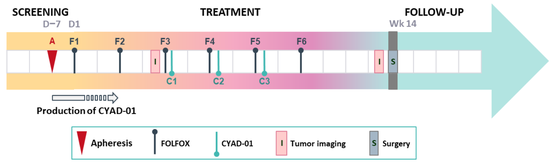


TABLE 1: SHRINK key eligibility criteria

Inclusion criteria	Exclusion criteria
• Histologically confirmed CRC	• Extra-hepatic metastases, except for ≤2 pulmonary metastases that are potentially resectable
• Planned neoadjuvant treatment with FOLFOX as first-line metastatic chemotherapy regimen	• Insufficient bone marrow reserve, hepatic or renal function
• Potentially resectable 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: SHRINK study endpoints

	Dose escalation phase	Expansion phase
Primary	– Occurrence of dose-limiting toxicity	– ORR prior to resection
Secondary	– Additional safety parameters – ORR prior to resection	– Safety – Multiple activity endpoints
Correlative	– Kinetics of CYAD-01 in peripheral blood – Systemic cytokines post-CYAD-01 treatment – NKG2D ligand expression in tumor samples pre- and post-treatment – Characterization of TME and CYAD-01 tumor infiltration	

ORR, objective response rate

References

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SHRINK Study Rationale

- An ongoing, multinational, open-label, dose escalation phase 1 trial in patients with advanced hematological and solid malignancies, THINK (NCT03018405), is investigating the safety and clinical activity of CYAD-01, administered as 3 doses at 2-week intervals, as stand-alone therapy without prior lymphodepleting preconditioning or bridging therapy [4, Poster CT129]
- Concurrent treatment with standard chemotherapy may improve the efficacy of CYAD-01 in solid tumors by:
  - Improving CYAD-01 expansion and persistence, owing to the lymphodepletion induced by chemotherapy
  - Increasing NKG2D ligand expression on tumor tissues targeted by CYAD-01
  - Increasing CYAD-01 tumor infiltration
  - Improving disease control due to the direct cytotoxic effect of chemotherapy administered prior to and concurrently with CYAD-01 infusion

SHRINK Trial Design

- SHRINK (**S**tandard c**H**emotherapy **R**egimen and **I**mmunotherapy with **NK**R-2, NCT03310008) is an open-label, phase 1 clinical trial designed to investigate the safety and activity of CYAD-01 administered concurrently with standard neoadjuvant chemotherapy in CRC patients with potentially resectable liver metastases
- The study consists of a dose escalation phase followed by a dose expansion phase at the recommended dose level (RecD)
  - The dose escalation will assess CYAD-01 at 3 dose levels (1×10^8, 3×10^8, and 1×10^9 CYAD-01 cells/injection) according to a standard 3+3 design to determine the maximum tolerated dose and the RecD
  - The dose expansion will further evaluate safety and activity of CYAD-01 at the RecD in 21 additional patients
- Patients will receive 6 doses of FOLFOX (folinic acid + fluorouracil + oxaliplatin) every 2 weeks, and 3 doses of CYAD-01 every 2 weeks starting at cycle 3, followed by resection of liver metastases 2–6 weeks after the end of the last chemotherapy cycle (**Figure 3**)
- 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, after 2 cycles of FOLFOX, and after all study treatment cycles
- Tumors will be biopsied at baseline and resection
- CYAD-01 and cytokines will be quantified in peripheral blood
- CYAD-01 will be quantified in hepatic metastases

Study Sites and Dates

- The first patient was recruited in February 2018
- Patients are currently being enrolled at sites in Belgium
- The estimated primary completion date for the dose escalation is May 2019