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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COLORECtAL CANCER (CRC)

1.4M new cases per year 
3rd most common cancer in men
2nd most common cancer in women

50% of patients develop metastases
Liver is the most frequent site of metastases

100% express NKG2D ligand

90–90% eligible for surgery

Intra-arterial delivery of therapy may enable clinical activity and minimize toxicity

CYAD-01 (previously named NKR-1) 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 stress-inducible ligands frequently expressed on various cancer cells [1,2]:
- MIC class I (MICA/B) and NKG2D-Ligand
- Unique long binding protein (ULBP) 1–4 ligands

The CYAD-01 CAR is composed of the full-length human NKG2D fused to the CD3 epsilon cytoplasmic signaling domain (Figure 1).

The surface adapter molecule CD3a-activating protein of lL15a (DAP-10), which is endogenously expressed in T cells, associates with and stabilizes CYAD-01 CAR expression. Ligand binding to CYAD-01 triggers a primary signal via CD3 and a secondary signal via DAP-10, resulting in efficient T-cell activation and cytokine secretion (Figure 2).

CYAD-01 showed promising results in multiple preclinical models and in the clinic [3, Poster CT134].

Preclinical results indicate that CYAD-01 may have anti-tumor effects beyond direct cancer cell killing:
- Targeting neoantigen expression using 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 myelocytes and myeloid cells within the tumor stroma, causing a shift from an immunosuppressive to an immunostimulatory TME

CYAD-01 is being explored as a long-term memory immune response specifically 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 3).

FIGURES AND TABLES

TABLE 1: Key eligibility criteria

Table with criteria for inclusion and exclusion.

TABLE 2: Study endpoints

Table with primary and secondary endpoints.

FIGURE 1: CYAD-01 CAR construct

Diagram showing the CYAD-01 CAR construct.

FIGURE 2: CYAD-01 clinical development

Diagram illustrating the clinical development of CYAD-01.

FIGURE 3: CYAD-01 CAR T CELL THERAPY

Diagram depicting the therapy of CYAD-01 CAR T cells.

LINK STUDY RATIONALE

- CAR T cells targeting solid tumors face additional obstacles compared to those targeting hematological malignancies [10,11]:
  - Tissue-specific, dense tumor and stromal stroma
  - Intra-tumoral, low pH, and low nutrient conditions
  - Immunosuppressor 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:
    - Increasing hormone of CYAD-01 to tumors, benefiting 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 distant lesions (abscopal effect)
    - Allowing the administration of higher doses compared to systemic delivery

LINK TRIAL DESIGN

- In (multifocal immunotherapy with NKG2D CAR T cells) is an open-label, dose escalation, phase 1 trial designed to assess the safety and clinical activity of CYAD-01 infused by hepatic transarterial administration in CRC patients with unresectable liver metastases.
- Patients will receive 3 doses of CYAD-01 at 2-week intervals (Figure 3).
- CYAD-01 will be assessed at 3 dose levels (1×107, 1×108, and 3×108 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 every week thereafter.

- Tumors will be assessed at baseline, 2 weeks post-CYAD-01 treatment, and at the time of hepatic metastases resection, if applicable.
- CYAD-01 and cytokines will be quantified in peripheral blood

- 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 2020.