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

Anne Flamant 1, Alain Hendiis 2, Leila Shaza 2, Sandrine Aspeslagh 2, Michaël Vouche 3, Vincent Donckier 2, Ahmad Awada 4, Jean-Pascal H. Machiels 4, Marc Van Den Eynde 4, Javier Carrasco 5, Caroline Lonez 1 and Frederic F. Lehmann 1.

1Celyad, Mont-Saint-Guibert, Belgium; 2Medical Oncology Clinic, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium; 3Department of Radiology, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium; 4Cliniques Universitaires Saint-Luc and Institut de Recherche Clinique et ExperimConf. (Pole MIPO), Université Catholique de Louvain, Brussels, Belgium; 5Service d’Oncologie-Hématologie, Site Notre-Dame, Grand Hôpital de Charleroi, Charleroi, Belgium

**LINK & SHRINK BACKGROUND AND STUDY RATIONALES**

- **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 bradytrophic, hypoxic, low pH, and low nutrient conditions) and overcome the hostile immune microenvironment (TME).

**CYAD-01 CAR T-CELL THERAPY**

- The **CYAD-01** CAR T-cell therapy is currently evaluated in the ongoing **THINK study (NCT03018405)** without preconditioning.

**The CYAD -01 CLINICAL DEVELOPMENT**

- **Preclinical results:** CYAD-01 may have anti-tumor effects beyond direct cancer cell killing ([1]).
- **Clinical development plan:** CYAD-01 is being evaluated in multiple settings (Figure 2).

**SHRINK STUDY DESIGN & STATUS**

- **The SHRINK study** consists of a dose escalation which assesses 3 dose levels of CYAD-01 (1×10^9, 1×10^10 and 3×10^10 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.
- Patients must have a histologically proven adenocarcinoma of the colon or rectum with unmetastasable liver metastases and:
  - Measurable hepatic metastases defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1,
  - No evidence of extra-hepatic metastases, with the exception of completely resectable pulmonary metastases,
  - Due to receive FOLFOX chemotherapy,
  - Measurable disease by RECIST version 1.1.
- Patients must have either:
  - A histologically proven colorectal adenocarcinoma with resectable liver metastases and measurable disease by RECIST version 1.1, or
  - No evidence of extra-hepatic metastases, with the exception of completely resectable pulmonary metastases.
- **Study Period:** The estimated primary completion date is Q3 – 2019.

**LINK STUDY DESIGN & STATUS**

- **The LINK (Locolregional Immunotherapy with NKG2D-2, NCT03101008) study** is an open-label, phase 1 clinical trial designed to investigate the safety and clinical activity of multiple CYAD-01 treatments i.v. administered at specific times within the chemotherapy cycles.
- **Study Period:** The estimated primary completion date is Q3 – 2019.

**LINK SHRINK MECHANISM of ACTION**

- A lower systemic toxicity and higher and more persistent concentration of the infused cells on the TME compared to systemic administration.
- Direct delivery and 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.

**LINK SHRINK STUDY RATIONALE**

- **The LINK (Locolregional Immunotherapy with NKG2D-2, NCT03101008) study** is an open-label, phase 1 clinical trial designed to investigate the safety and clinical activity of multiple CYAD-01 treatments i.v. administered at specific times within the chemotherapy cycles.
- **Study Period:** The estimated primary completion date is Q3 – 2019.

**LINK STUDY RATIONALE**

- **The LINK (Locoregional Immunotherapy with NKG2D-2, NCT03101008) study** is an open-label, phase 1 clinical trial designed to investigate the safety and clinical activity of multiple CYAD-01 treatments i.v. administered at specific times within the chemotherapy cycles.
- **Study Period:** 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 (1×10^10, 1×10^11, and 3×10^11 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 at least 3 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 cycle.
- **Study Period:** The first patient was recruited in Q1 – 2018.

- **The estimated primary completion date is Q3 – 2019.**

**SHRINK STUDY RATIONALE**

- The **SHRINK (Standard Chemotherapy Regimen and Immunotherapy with NKG2D-2, NCT03370198) 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 anchor to the lymphoid area induced by the FOLFOX,
  - Increase the NKGD IgG expression in tumor tissues targeted by CYAD-01, and
  - Improve the disease control due to the direct cytolytic effect of chemotherapy administered prior to and concurrently with CYAD-01 infusion.

**SHRINK STUDY DESIGN & STATUS**

- The **SHRINK study** consists of a dose escalation which assesses 3 dose levels of CYAD-01 (1×10^10, 1×10^11, and 3×10^11 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 at least 3 additional patients.
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