SO – 009 Phase 1 studies assessing the safety and clinical activity of autologous and allogeneic NKG2D-based CAR-T therapy in metastatic colorectal cancer

E Van Cutsem[1], J Machiels[2], M Van den Eynde[3], H Prenen[4], A Hendlisz[5], L Shaza[5], J Carrasco[6], J Canon[7], P Sotiropoulou[8], E Breman[8], E Alcantar[8], A Flament[8]

[1]University Hospitals Gasthuisberg, Leuven and KU Leuven, Leuven, Belgium, [2]St-Luc University Hospital, Brussels, Belgium, [3]Clin. Univ. St-Luc Bruxelles, Brussels, Belgium, [4]University Hospital Gasthuisberg, Leuven, Belgium, [5]Institut Jules Bordet, Brussels, Belgium, [6]Grand Hôpital de Charleroi, Charleroi, Belgium, [7]Service d'Oncologie-Hématologie, Grand Hôpital de Charleroi, Charleroi, Belgium, [8]Celyad, Mont-Saint-Guibert, Belgium

Introduction: Chimeric antigen receptor T-cell (CAR-Ts) therapies have yet to demonstrate positive results in the context of solid tumors mainly because of the difficulty of CAR-T cells to access the site of metastases and to overcome a hostile immunosuppressive tumor microenvironment (TME). NKG2D receptor-based CAR T-cells target 8 stress ligands expressed in both hematological and solid tumors. Reports of remissions in relapsed/refractory acute myeloid leukemia and stabilization in metastatic colorectal cancer (mCRC) patients treated with the autologous NKG2D CAR (CYAD-01) as a standalone therapy provide confidence in the relevance of these targets.

Methods: Two NKG2D CAR products are investigated in mCRC patients in two separate studies. The SHRINK study (NCT03310008) evaluates the autologous product CYAD-01 while the alloSHRINK study (NCT03692429) evaluates an allogeneic analog of CYAD-01, i.e. CYAD-101. Both studies evaluate the safety and clinical activity of multiple infusions of the NKG2D CAR T-cells administered concurrently to the standard of care FOLFOX chemotherapy through a 3 + 3 design evaluating 3 dose levels (DL) of the NKG2D CAR T-cells: 1x10 8, 3x10 8 and 1x10 9 T-cells per infusion. The concurrent administration of FOLFOX aims at improving the likeliness of clinical responses in solid tumors by (i) favoring infiltration into and overcome the immunosuppressive TME, (ii) improving engraftment of CAR T-cells due to the lymphodepletion induced by the chemotherapy, and likely (iii) increasing the NKG2D ligand expression in tumor tissues targeted by the NKG2D CARs. In the context of the CYAD-101 allogenic administration, while the GvHD effect is controlled by the inhibition of TCR signaling in the study product, the FOLFOX administration will also contribute to control the host-versus-graft (HvG) reaction through elimination of the previously adoptively-transferred CYAD-101 cells.

Results: As of March 2019, 8 patients have been enrolled in the three DL of SHRINK (3 at DL-1, 3 at DL-2 and 2 at DL-3). DL-1 and 2 have been completed without any dose-limiting toxicity (DLT) occurrence, nor Grade 3/4 related adverse events (AE) occurrence (uncleaned database). DL-3 should be completed by June 2019. 6 patients have been enrolled in the first two DL of alloSHRINK (3 at DL-1 and 3 at DL-2) without any

DLT, treatment-related AEs nor graft-versus-host disease (GvHD) occurrence as of March 2019. Enrollment into DL-3 should be completed by June 2019.

Conclusion: Safety, clinical and translational research data comparing autologous and allogeneic approaches at the end of the dose-escalations will be presented, including any potential difference in terms of cell engraftment. These studies will provide critical information to support the development of CAR-T therapy in solid tumors.