NKG2D-based CAR-T therapy in a Multinational Phase 1 Dose Escalation and Expansion Study Targeting Multiple Solid and Hematologic Tumor Types.

AUTHORS: Bikash Verma1, Philippe Aftimos2, Ahmad Awada3, Jean-Pascal H. Machiels3, Jason B. Brayer4, David A Sallman5, Tessa Kerre6, Kunle Odunsi7, Caroline Lonez8, David Edward Gilham8, Frederic Lehmann8. 1Celyad, Boston, MA; 2Medical Oncology Clinic, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium; 3Institut Roi Albert II, Service d’Oncologie Médicale, Cliniques Universitaires Saint-Luc and Institut de Recherche Clinique et Expérimentale (Pole MIRO), Université Catholique de Louvain, Brussels, Belgium; 4H Lee Moffitt Cancer Ctr and Rsrch Inst, St Petersburg, FL; 5Moffitt Cancer Center, Tampa, FL; 6Ghent University Hospital, Ghent, Belgium; 7Roswell Park Cancer Institute, Buffalo, NY; 8Celyad, Mont-Saint-Guibert, Belgium.

BACKGROUND: Chimeric Antigen Receptor (CAR)-T therapy has potentially serious limitations related to target antigen loss, toxicity due to pre-conditioning regimen, and lack of activity in many tumor types. To overcome these limitations, we have developed a novel CAR-T, called NKR-2, incorporating the full-length human natural killer receptor NKG2D fused with the human CD3 zeta signaling domain. When expressed in T-cells, the naturally-expressed DAP10 provides co-stimulatory signals to NKR-2 to produce cytokines and selectively target tumor cells upon recognition of up to 8 different stress-induced NKG2D ligands expressed in many solid and hematologic malignancies. In preclinical studies, NKR-2 demonstrated long-term anti-tumor activity towards a breadth of tumor indications, in the absence of pre-conditioning, whilst simultaneously targeting tumor cells and cells from the local tumor neo-vasculature and suppressive immune environment. In our recently completed First-in-Human Phase 1 study (NCT02203825) in hematologic cancers, a single administration of autologous NKR-2 was safe with initial signs of clinical benefit.

METHODS: Exploiting the multiple ligand targeting capability and unique mode of action of NKR-2, the THINK trial (THERapeutic Immunotherapy with NKR-2) is an open-label Phase I study that will assess the safety and clinical activity of multiple infusion NKR-2 treatment (every 2 weeks x 3 infusions) in relapse/refractory patients with metastatic or locally advanced CRC, urothelial carcinoma, TNBC, pancreatic cancer, recurrent epithelial ovarian and fallopian tube carcinoma, AML/MDS and MM, post standard treatment. The study contains two consecutive segments. The dose escalation segment will enroll 18 patients in two separate hematologic and solid malignancy arms, and will evaluate 3 dose levels of NKR-2 (3x10⁸, 1x10⁹ and 3x10⁹ per injection) following a 3+3 design. The expansion segment will then enroll 96 additional patients in 7 separate cohorts for each indication with 3 steps of statistical analysis (overall futility, cohort futility and final evaluation). The study is open for recruitment in both EU and US (NCT03018405).
ABOUT CELYAD: Celyad is a clinical-stage biopharmaceutical company focused on the development of specialized cell-based therapies. The Company utilizes its expertise in cell engineering to target cancer. Celyad’s Natural Killer Receptor based T-Cell (NKR-T) platform has the potential to treat a broad range of solid and hematologic tumors. Its lead oncology candidate, the CAR-T NKR-2, has been evaluated in a single dose - escalation Phase I clinical trial to assess the safety and feasibility of CAR-T NKR-2 cells in patients suffering from AML or MM. This Phase I study was successfully completed in September 2016. Celyad was founded in 2007 and is based in Mont-Saint Guibert, Belgium, and Boston, Massachusetts. Celyad’s ordinary shares are listed on the Euronext Brussels and Euronext Paris exchanges, and its American Depositary Shares are listed on NASDAQ Global Market, all under the ticker symbol CYAD.