A Phase I Global Trial Targeting Multiple Solid and Hematologic Malignancies through a NKG2D receptor-based CAR-T Immunotherapy

1210TiP

Bikash Verma[1], Ahmad Awada[2], Philippe Aftimos[2], Philippe Lewalle[2], Nathalie Meuleman[2], Jean-Pascal H. Machiels[3], Gaetan Catala[3], Eric Vandenneste[3], Jason B. Brayer[4], David A Sallman[4], Solmaz Sahebjam[4], Tessa Kerre[5], Sylvie Rottey[5], Kunle Odunsi[6], Eunice S. Wang[6], Urmila Santanam[1], Caroline Lonez[7], David Edward Gilham[7], Frederic Lehmann[7]

ABSTRACT

BACKGROUND: Because of its increasingly demonstrative successes, CAR-T therapy has been well recognized as one of the most promising therapies for cancer. We have developed a novel autologous CAR-T, 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 the co-stimulatory signals to NKR-2 to be fully activated. NKR-2 selectively target tumor cells upon recognition of up to eight different NKG2D ligands expressed in many distinct cancer indications. In preclinical studies, NKR-2 demonstrated long-term anti-tumor activity towards multiple solid and hematologic tumors deploying multiple mechanisms of action targeting tumor cells and cells from the neo-vasculature and tumor suppressive immune environment, resulting in an adaptive response. In our recently completed Phase 1 study in hematologic cancers, a single administration of autologous NKR-2 was safe with initial signs of clinical benefit. Likewise, to overcome the operational challenges, our trial design incorporates strategies to harmonize multiple clinical and manufacturing processes while also enhancing patient safety and clinical outcomes.

TRIAL DESIGN: THINK trial (THerapeutic Immunotherapy with NKR-2) is a EU/US open-label Phase I study to assess the safety and clinical activity of NKR-2 therapy administered in three infusions, two weeks apart in five solid tumor indications (CRC, urothelial, TNBC, pancreatic, ovarian) and two hematologic indications (AML/MDS and MM). No lymphodepleting conditioning is required in this study. The study contains two consecutive segments. The dose escalation segment will enroll 18 patients in two separate hematologic and solid malignancy arms, and evaluate 3 dose levels of NKR-2 ($3x10^8$, $1x10^9$ and $3x10^9$ cells 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, futility within each cohort and final evaluation). At time of submission, the trial has completed enrollment in its first cohort among solid indications.

NKR-2 CAR T-CELLS

- NKR-2 CAR T-cells are autologous T-cells genetically modified to express a CAR comprising a fusion of the full-length human NKG2D receptor (an activating receptor expressed mainly in humans on NK cells) with the CD3ζ signaling domain (**Figure 1**).
- The NKR-2 actually works like a 'second generation' CAR, thanks to the association of NKG2D with DAP10, constitutively expressed on T-cells, which provides a co-stimulatory signal complementing the primary CD3ζ signal.
- NKR-2 construct consists entirely of human sequences allowing multiple NKR-2 injections without the anticipated risk to induce an humoral immune response.
- In humans, NKG2D targets eight ligands: the major histocompatibility class (MHC) class I chain related proteins (MICA and MICB) and the unique long 16 binding proteins (ULBPs 1 to 6) [1].
- A broad range of tumors express NKG2D ligands [2, 3] including hematological and solid tumor types [3], while NKG2D ligands are absent or lowly expressed in healthy tissues [2, 3].
- NKR-2 CAR T-cells mediate potent anti-tumor activity *in vitro* and *in vivo*, without prior lymphodepleting pre-conditioning [6] against both hematological (lymphoma, multiple myeloma) and solid (ovarian cancer, melanoma and pancreatic cancer (**Figure 2**)) tumor models [4].

FIGURES & TABLES

FIGURE 1: NKR-2 construct

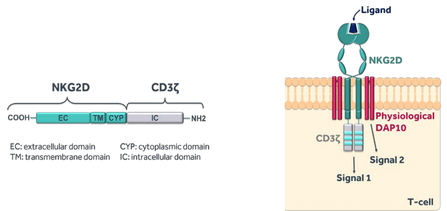
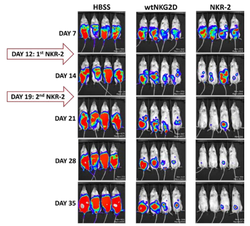


FIGURE 2: Preclinical data on human pancreatic cancer model



NSG mice were injected intraperitoneally (IP) with 0.5 x 10^6 luciferase-expressing PANC-1 tumor cells and tumor engraftment was followed by bioluminescent imaging (N=1). Twelve and nineteen days after PANC-1 injection, control mice received either HBSS buffer (HBSS group), $5x10^6$ of T cells (IP) retrovirally transduced with the wild-type NKG2D (wtNKG2D T-cells) or with the NKR-2 construct (NKR-2 group). Imaging was performed every week starting one week after tumor inoculation. Thirty-five-days post tumor injection, the final imaging showed that some mice that received the NKR-2 treatment had little tumor remaining compared to HBSS and wtNKG2D groups where mice had a large tumor burden [5].

FIGURE 3: NKR-2 mechanisms of action

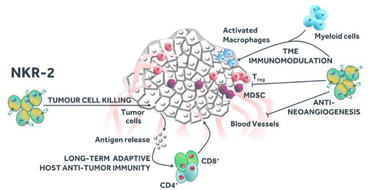


FIGURE 4: NKR-2 manufacturing process

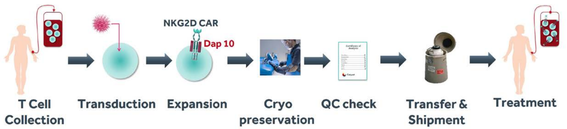
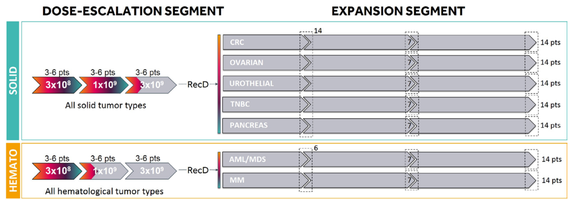


FIGURE 5: Overview of the THINK study design



RecD: recommended dose

Overall futility
Stop study in
- Solid if ORR = 0/14
- Hemato if ORR = 0/6

Indication futility
Stop one indication if ORR = 0/7

Final evaluation
Success in one indication if ORR ≥ 3/14

TABLE 1: Eligibility criteria

Main eligibility criteria	Disease-specific inclusion criteria
• Men or women ≥ 18 years old at the time of signing the ICF. • Patient with specific cancer indications. • Disease must be measurable according to the corresponding guidelines. • No tumor metastasis in the central nervous system. • ECOG performance status of 0 or 1 or 2 based on peripheral neuropathy from prior therapies. • Patient with adequate bone marrow reserve, hepatic and renal functions. • Left ventricular ejection fraction of > 40%. • Tumor biopsy at baseline. • No previous cancer therapy within 2 weeks before the planned day for the apheresis. • No administration of concurrent growth factor, systemic steroid, other immunosuppressive therapy or cytotoxic agent. • No major surgery within 4 weeks before the planned day for the first NKR-2 administration.	• Metastatic or locally advanced colorectal adenocarcinoma after at least 2 prior standard cancer therapy regimens. • Recurrent epithelial ovarian cancer or fallopian tube carcinoma after at least 2 prior standard cancer therapy regimens. • Inoperable locally advanced or metastatic urothelial carcinoma after previous platinum-based chemotherapy. • Metastatic or locally advanced triple-negative breast cancer after at least 1 prior cancer therapy regimen. • Metastatic or locally advanced pancreatic ductal adenocarcinoma with a maximum of 2 prior lines of standard therapy regimens. • Relapsed or refractory AML after one prior standard therapy. No previous allograft. • Intermediate, High-risk or Very High-risk myelodysplastic syndrome or refractory anemia with excess blasts by WHO or MDS with TP53 mutation with at least one prior treatment with at least 4 cycles of azacitidine or decitabine. • Relapsing or refractory/relapsing multiple myeloma with at least 1 prior line of systemic therapy, including prior exposure to both proteasome inhibitor (PI) and immunomodulatory drug.

THINK TRIAL DESIGN & STATUS

THINK study (NCT03018405, EudraCT 2016-003312-12) key design aspects:

- Open-label and multinational (EU and US) phase I study with two consecutive segments (**Figure 5**).
- NKR-2 treatment administered three times every 2 weeks
- Three dose-levels: $3x10^8$, $1x10^9$ and $3x10^9$ NKR-2 cells/injection.
- Five solid and two hematological tumor indications (**Table 1**).
- No prior lymphodepletion.
- NKR-2 is supplied cryopreserved in bags containing a T-cell dose in accordance with the dose-level which is to be administered with a centralized production center (**Figure 4**).

Main objectives:

- A first dose escalation segment (3+3 design) evaluating the feasibility and safety of NKR-2 aiming at determining the recommended dose (RecD) of NKR-2 cells separately for solid or hematological tumor types based on the occurrence of dose limiting toxicities (DLTs) during the study treatment until 14 days after the 3rd NKR-2.
- A second segment extending the safety study at the RecD and investigating initial clinical activity of NKR-2 across the seven tumor indications, separately. This segment is split in three steps with intermediate futility and safety evaluations, allowing the RecD to be still adapted according to predefined safety rules in any specific tumor type.

Current status (Figure 5):

- Dose-level 3 in solid indications.
- Dose-level 2 in hematologic indications.
- Feasibility and safety – no DLTs to date.

PERSPECTIVES

Preclinical data suggest **four different mechanisms of action** of NKR-2 (**Figure 3**) :

- Direct cytotoxicity against cancer cells,
- Anti-angiogenic activity potentially through targeting of NKG2D ligands expressed upon tumor neovasculature [7],
- Modulation of the immune tumor microenvironment through direct targeting of immunosuppressive myeloid-derived suppressor cells (MDSCs) and regulatory T-cells (Tregs), and recruitment of myeloid cells and activated macrophages [8, 9],

All together resulting in:

- The generation of a tumor-specific adaptive immune response capable of protecting against tumor re-challenge, despite relatively short-term circulation of NKR-2 T-cells themselves [8-10].

Exploiting the targeting of NKG2D ligands by NKR-2 CAR-T therapy to fight against solid and hematologic tumor indications with a single generic construct combining two features of innate and adaptive immunity, provides potentially a new paradigm for CAR T-cell therapy that the current protocol is designed to investigate.

AFFILIATIONS: [1]Celyad, Boston, MA, USA; [2]Medical Oncology Clinic, Institut Jules Bordet, Brussels, Belgium; [3]Service d'Oncologie Médicale, Cliniques Universitaires Saint-Luc and Institut de Recherche Clinique et Expérimentale, Brussels, Belgium; [4]H Lee Moffitt Cancer Center and Research Inst, Tampa, FL; [5]Ghent University Hospital, Ghent, Belgium; [6]Roswell Park Cancer Institute, Buffalo, NY; [7]Celyad, SA, Mont-Saint-Guibert, Belgium

REFERENCES:

[1]. Carapito R, Bahram S. Immunol Rev 2015;267(1):88–116.
[2]. Le Bert N, Gasser S. Immunol Cell Biol 2014;92(3):230-6.
[3]. Spear P, et al. Cancer Immunity Archive 2013;13:8.
[4]. Sentman CL, Meehan KR. Cancer J 2014;20(2):156-9
[5]. Demoulin B, et al. Future Oncology 2017;In Press.
[6]. Barber A, et al. Gene Ther 2011;18(5):509-16.
[7]. Zhang T, Sentman CL. J Immunol 2013;190(5):2455-63.
[8]. Barber A, et al. J Immunol 2009;183(11):6939-47.
[9]. Spear P, et al. J Immunol 2012;188(12):6389-98.
[10]. Spear P, et al. Oncoimmunology 2013;2(4):e23564.