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

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ABSTRACT

BACKGROUND: NKG2D is a Group III C-type lectin receptor that recognizes stressed and/or infected cells in cooperation with CD94/NKG2A/2C. 

METHODS: Explore the first-in-human dose escalation and expansion study of NKG2D CAR T cells in solid tumors. The study is a multicenter, open-label, dose escalation study with a 3+3 design. Patients must have refractory solid tumors with confirmed Ki67 of ≥30%.

RESULTS: NKG2D CAR T cells were well tolerated with dose-limiting toxicities (DLTs) at the 86 mg/m² dose level. No grade 4 or 5 toxicities were observed.

CONCLUSION: Further evaluation of NKG2D CAR T cells in solid tumors is warranted.

FIGURES & TABLES

FIGURE 1: Preclinical data on human pancreatic cancer model

FIGURE 2: NKR-2 manufacturing process

FIGURE 3: Overview of NKR-2 manufacturing process

FIGURE 4: Overview of THINK study procedures

TABLE 1: Eligibility criteria

TBP3093

THINK trial design & status

THINK study NCT02164649, Safety/Toxicity Study

Phase I with a 3+3 dose-escalation

- NKR-2 treatment administered three times every 4 weeks

- Three dose levels: 50 mg/kg, 75 mg/kg, and 100 mg/kg

- Toxicology and immunological tumor markers

- Risk vs benefit

- Prior lymphodepletion

- NKR-3 is supplied cryopreserved in bags containing a T-cell dose in accordance with the dose range which is to be administered to the patient on a centralized production facility (Figure 4).

Main objectives:

- A first dose-escalation segment (1-3) designed evaluating the feasibility and safety of NKR-3 aiming at determining the recommended dose (RdC) of NKR-3 cells separately for solid and hematologic tumor types based on safety, tolerability, and pharmacokinetics (PK) (e.g., via T-cell recovery (T-cell recovery) during the treatment period).

- A second segment extending the safety study at the Rdc and investigating initial clinical activity of NKR-3 across the seven tumor indications.

Toxicities

- Dose levels in solid indications and hematologic indications.

- Feasibility and safety will be determined.

Explanations: NKG2D CAR T cells are designed to recognize and kill NKG2D-expressing tumor cells, which include a wide range of solid tumors. The NKG2D CAR T cells have shown promising results in preclinical studies and have been well tolerated in early clinical trials.

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For solid tumors:

- Recurrence of solid tumors
- Adequate organ function
- No prior lymphodepletion

For hematologic malignancies:

- Presence of refractory hematologic malignancies
- Adequate organ function
- No prior lymphodepletion

Primary endpoint: Overall response rate in solid tumors

Secondary endpoints:

- Safety and tolerability
- Pharmacokinetics
- Immunological tumor markers

References:


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