DUET-01: A first-in-human, phase 1/2 study of BOXR1030 in patients with advanced glypican-3-positive solid tumors

TPS2681

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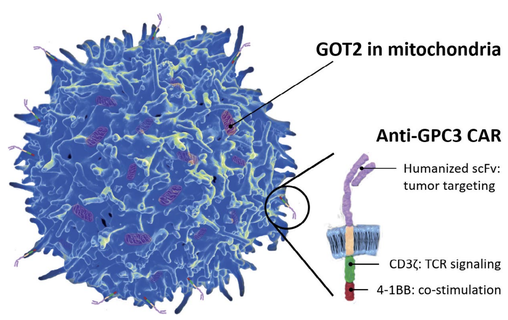
- Open-label, dose escalation and expansion ***clinical trial (NCT05120271)***
- To determine a ***safe dose of CAR-T cell therapy BOXR1030***
- To determine the preliminary ***antitumor activity of BOXR1030***
- In patients with ***advanced GPC3-positive solid tumors***

Background

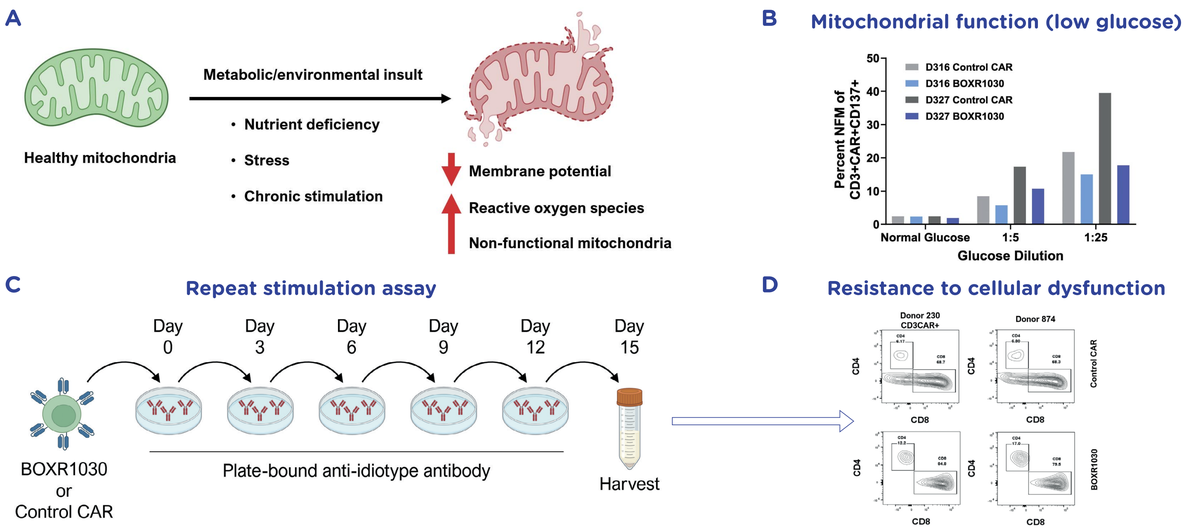
BOXR1030 is an autologous T-cell therapy co-expressing a chimeric antigen receptor (CAR) targeting glypican-3 (GPC3) and glutamic-oxaloacetic transaminase 2 (GOT2).

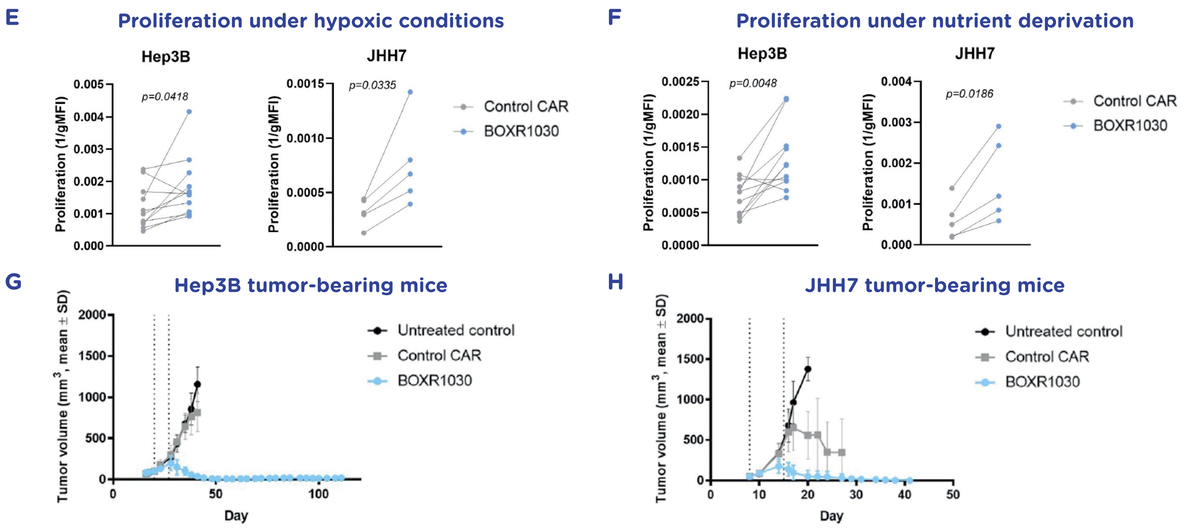
- **GPC3:** Membrane-bound heparin sulfate proteoglycan involved in cell proliferation overexpressed in several tumor types[1]; GPC3 expression observed in >30% of samples from patients with hepatocellular carcinoma, squamous cell carcinoma of the lung, myxoid/round cell liposarcoma and Merkel cell carcinoma, demonstrating its attractiveness as a CAR tumor antigen target[2]
- **GOT2:** Mitochondrial enzyme playing an important role in maintaining mitochondrial function and improving T-cell functionality in the solid tumor microenvironment[3-5]



Preclinical data

- BOXR1030 T cells have improved metabolism and survival under conditions simulating stressors within the tumor microenvironment as compared to traditional CAR T cells.[2,6]





(A) Model highlighting various environmental and metabolic stressors resulting in non-functional mitochondria (NFM). **(B)** Cells were activated with Hep3B tumor spheroids in normal glucose (37 mM) or low glucose (1:5 diluted = 7.4 mM, 1:25 diluted = 1.48 mM) conditions for 7 days. Activated (CD137⁺) CAR⁺ cells were assessed for NFM. Results from 2 donors are shown. **(C)** Schematic representing repeat stimulation of BOXR1030 and control CAR⁺ T cells with anti-idiotype antibody-coated plates. **(D)** Frequency of CD4⁺ and CD8⁺ populations were assessed in BOXR1030 or control CAR⁺ T cells following 5 repeated stimulations over 15 days. Representative flow plots are shown. **(E and F)** BOXR1030 or control CAR⁺ T cells were repeat stimulated with GPC3⁺ target cell lines on day 0 and on day 3 in hypoxic conditions **(E)** or low glucose conditions **(F)**. The geometric mean fluorescence intensity (gMFI) of CellTrace Violet was measured for BOXR1030 and control CAR⁺ T cells stimulated with target cells on day 7 in the indicated culture conditions and proliferation was plotted as 1/gMFI (n = 5 for JHH7 stimulated conditions and n = 11 for Hep3B stimulated conditions; statistical analysis was performed using a paired t-test, and p-values < 0.05 were considered statistically significant). **(G)** Hep3B tumor-bearing mice (mean tumor volume 108.7 ± 34.1 mm^3) were treated with 2 weekly doses of 1 × 10^6 control CAR⁺ or BOXR1030 T cells each (total dose of 2 × 10^6 CAR⁺ cells; dosing days indicated by dotted lines), and tumor volumes were measured over the course of 110 days. Plots were discontinued when less than 50% of group was remaining. **(H)** JHH7 tumor-bearing mice (mean tumor volume 49.8 ± 7.2 mm^3) were treated with 2 weekly doses of 5 × 10^6 control CAR⁺ or BOXR1030 T cells each (total dose of 10 × 10^6 CAR⁺ cells; dosing days indicated by dotted lines), and tumor volumes were measured out to 50 days. Plots were discontinued when less than 50% of group was remaining.

References:

[1] Moek KL et al. Glypican 3 overexpression across a broad spectrum of tumor types discovered with functional genomic mRNA profiling of a large cancer database. Am J Pathol. 2018;188(9):1973-1981. [2] Hickman TL et al. BOXR1030, an anti-GPC3 CAR with exogenous GOT2 expression, shows enhanced T cell metabolism and improved anti-cell line derived tumor xenograft activity. PLoS One. 2022;17(5):e0266980. [3] Bailis W et al. Distinct modes of mitochondrial metabolism uncouple T cell differentiation and function. Nature. 2019;571(7765):403-407. [4] Bettonville M et al. Long-term antigen exposure irreversibly modifies metabolic requirements for T cell function. Elife. 2018;7. [5] Chisolm DA et al. CCCTC-binding factor translates interleukin 2- and α-ketoglutarate-sensitive metabolic changes in T cells into context-dependent gene programs. Immunity. 2017;47(2):251-267.e257. [6] Hinds J et al. 238 Exogenous GOT2 in CAR-T cells improves metabolic function and preserves early memory T cell subsets. J Immunother Cancer. 2022;10(Suppl 2):A252-A252.

Key eligibility criteria

- Histologically confirmed advanced unresectable or metastatic hepatocellular carcinoma, squamous cell carcinoma of the lung, myxoid/round cell liposarcoma or Merkel cell carcinoma
- GPC3 overexpression by immunohistochemistry assay with a cytoplasmic/membranous H-score > 30 confirmed centrally on tumor specimen taken within 6 months prior to signing consent and after the initiation of the patient's most recent systemic anticancer therapy
- Body weight of ≥ 50 kg (≥ 65 kg for dose level 1)
- Life expectancy > 16 weeks

Endpoints

Primary

- Incidence of dose-limiting toxicities (DLTs)
- Determination of the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D)
- Type, frequency and severity of treatment-emergent adverse events; clinically significant abnormal safety laboratory findings and vital signs

Secondary

- Investigator-assessed responses defined according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 (objective response rate [ORR], best overall response, duration of response, progression-free survival, clinical benefit rate, time to response, time to progression); antitumor activity will be assessed every 6 weeks after BOXR1030 infusion
- BOXR1030 T-cell levels in blood
- BOXR1030 T-cell characterization in blood
- Levels of inflammatory markers including C-reactive protein, serum ferritin, erythrocyte sedimentation rate and triglycerides

Key exploratory

- Overall survival
- Levels of cytokines and other analytes in blood
- Incidence and severity of selected adverse events and detection of replication-competent retrovirus
- Investigator-assessed responses defined according to RECIST for immune-based therapeutics (iRECIST)
- BOXR1030 T-cell levels, phenotype and location in post-treatment tumor tissue
- Levels of anti-drug antibodies to BOXR1030

Study treatment

Screening and GPC3+ confirmation	Leuka-pheresis	BOXR1030 manufacturing	Lymphodepletion (fludarabine and cyclophosphamide)	BOXR1030 administration	DLT assessment	Post-treatment follow-up	Long-term follow-up
Within 30 days prior to enrollment	*After enrollment*	*Around 28 days*	*For 3 days within 5 days prior to BOXR1030*	*Day 1*	*Day 1 to Day 28*	*Day 1 to Month 6*	*Month 7 to Year 15*

Screening and GPC3⁺ confirmation

- Immunohistochemistry screening: Tumor biopsy informed consent to confirm GPC3 overexpression
- Study treatment screening: Main informed consent for the study

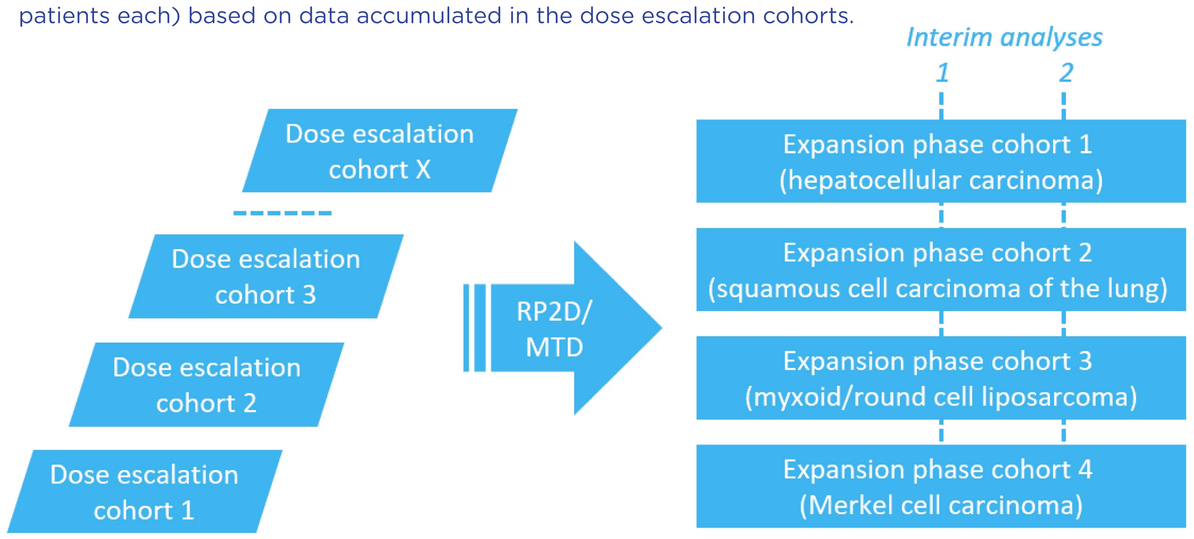
Lymphodepletion

- 300 mg/m^2/day of cyclophosphamide and 30 mg/m^2/day of fludarabine for 3 days within a 5-day window prior to BOXR1030 administration

Study design

Dose escalation cohort	BOXR1030 target dose
Cohort 1	0.3 × 10^6 BOXR1030 T cells/kg body weight
Cohort 2	0.9 × 10^6 BOXR1030 T cells/kg body weight
Cohort 3	2.7 × 10^6 BOXR1030 T cells/kg body weight
Cohort 4	8.1 × 10^6 BOXR1030 T cells/kg body weight
Cohort 5	16.2 × 10^6 BOXR1030 T cells/kg body weight

- The maximum dose to be administered will be 2,000 × 10^6 BOXR1030 T cells.
- The Dose Escalation Committee will select the RP2D to be used in the expansion phase cohorts (10-20 patients each) based on data accumulated in the dose escalation cohorts.



Statistics

- The MTD is the dose that maximizes the probability of targeted toxicity among doses that satisfy the escalation with overdose control criterion.
- The Bayesian logistic regression model will use the DLT data to estimate the MTD.
- Two interim analyses will determine futility by evaluating ORR using the posterior probability of futility.

Study status

- The first patient was treated with BOXR1030 in December 2022.

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