317 B7-H3-TARGETED CAR T CELL WITH AN INDUCIBLE CASPASE 9 SUICIDE GENE EFFECTIVELY ERADICATES UVEAL MELANOMA LIVER METASTASES

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Background Most uveal melanoma (UM) patients will develop metastatic disease to the liver. No effective therapies are currently available to treat metastatic UM (mUM). B7-H3/CD276 is an immune checkpoint molecule expressed in many tumors and notably, expressed at high levels in mUM. Here we investigated the preclinical efficacy of a Chimeric Antigen Receptor (CAR) T cell-based immunotherapy targeting B7-H3. Our B7-H3-specific CAR construct includes an inducible caspase 9 (iC9) suicide gene controlled by the chemical induced of dimerization AP1903 in case of an adverse reaction. This mechanism allows rapid and conditional elimination of iC9. B7-H3 CAR T cells.

Methods B7-H3 expression on human UM tissue samples and cell lines was assessed by immunohistochemistry and flow cytometry. iC9.B7-H3 CAR T cells were generated from healthy donors' peripheral blood mononuclear cells by transduction with a retroviral vector encoding a B7-H3-specifc CAR comprised of iC9 suicide gene and CD28 costimulatory domain. Antitumor activity of iC9.B7-H3 CAR T cells was tested *in vitro* with UM cell lines, mUM patient-derived organotypic tumor spheroids (PDOTS), and NSG mice.

Results High surface expression of B7-H3 was observed on human mUM tissue samples (n=6). Tested specimens demonstrated 50–100% (n=4) and 26–50% (n=2) of positively stained cells, with most (5/6) displaying moderate-strong intensity and only 1 demonstrating weak intensity of expression. Homogeneous B7-H3 expression was confirmed on primary and metastatic UM cell lines (n=6, 97 ± 6%). iC9.B7-H3 CAR T cells demonstrated specific and potent antitumor activity against UM cells at high and low E:T ratios (tumor killing: 90±5% at 1:1, 43±5% at 1:16), and complete eradication of B7-H3-expressing PDOTS. iC9.B7-H3 CAR T cells demonstrated robust expansion *in vivo* resulting in complete and sustainable eradication of UM liver metastases for over 120 days. Administration of AP1903 rapidly eliminated iC9.B7-H3 CAR T cells demonstrating the functionality of the iC9 safety-switch.

Conclusions Our study identified B7-H3 as a novel target for CAR T cell-based immunotherapy in mUM and demonstrates the preclinical efficacy of iC9.B7-H3 CAR T cells. Our findings strongly support the rationale for the design of a Phase I clinical trial to treat patients with mUM.

Ethics Approval Formalin-fixed paraffin-embedded tissue samples derived from surgically removed metastatic lesions of UM patients were collected under an Institutional Review Board (IRB) approved protocol and kindly provided by the Dr. G. Boland BioBank at Massachusetts General Hospital (MGH). Fresh mUM tumor samples from deidentified UM patients were obtained under Dana-Farber/Harvard Cancer Center IRB-approved protocols.

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