SENSITIZING POORLY DIFFERENTIATED THYROID CANCERS TO TSHR-CART CELL THERAPY WITH MEK INHIBITORS

John Copland, Kendall Schick, Justyna Gleba, Truc Huy, James Miller, Erin Miller, Alyin Alasonyilla Demirel, Erin Tapper, Reona Sakemura, Elizabeth Siegler, Michelle Cox, Carl Stewart, Ismail Can, Ekene Ogbo, Claudia Manriquez Roman*, Bezerra Evandro, Cui Gadang, Mer Georges, Oliver Gloria, Yushu Qui, Robert Smallridge, Abba Zubair, Han Tun, Saad Kenderian. Mayo Clinic, Jacksonville, FL, USA

Background Thyroid cancer incidence is rising,1 and most thyroid cancer deaths are attributed to a subset of de-differentiated, treatment-refractory, metastatic tumors. Thyroid stimulating hormone receptor (TSHR),2,3 making TSHR a compelling target for advanced thyroid cancer diagnostics and therapeutics. We therefore developed a novel TSHR-targeted chimeric antigen receptor (CAR) T cell therapy to treat these aggressive thyroid cancers.

Methods TSHR-CAR constructs were synthesized using a single chain variable fragment derived from thyroid auto-antibody clone KI70 and cloned into a lentiviral CAR construct containing 4BB and CD3ζ. We then generated TSHR-CART by transducing T cells derived from normal donors. TSHR-CART demonstrated potent antigen-specific in vitro and in vivo antitumor activity. NOD-SCID-γ/- (NSG) mice were inoculated subcutaneously with a TSHR-overexpressing thyroid cancer cell line, THJ529, and were randomized by tumor volume to treatment with TSHR-CART cells or control untransduced T cells (UTD). Treatment with TSHR-CART cells resulted in dose-dependent antitumor activity and prolonged survival (figure 1).

Results Anaplastic thyroid cancers (ATC) are reported to downregulate TSHR. Our TSHR immunohistochemistry results corroborated these findings and displayed attenuated or no TSHR protein expression, precluding successful TSHR-CART treatment (figure 2). We therefore sought to sensitize these tumors with mitogen-activated protein kinase (MEK) inhibitors, which have been shown to upregulate TSHR expression in patients with metastatic thyroid cancer.4,5 We then generated TSHR-CART by transducing T cells derived from normal donors. TSHR-CART demonstrated potent antigen-specific in vitro and in vivo antitumor activity. NOD-SCID-γ/- (NSG) mice were inoculated subcutaneously with a TSHR-overexpressing thyroid cancer cell line, THJ529, and were randomized by tumor volume to treatment with TSHR-CART cells or control untransduced T cells (UTD). Treatment with TSHR-CART cells resulted in dose-dependent antitumor activity and prolonged survival (figure 1).

Conclusions Collectively, our findings indicate that MEK/BRAF inhibition of de-differentiated thyroid cancers upregulated TSHR expression and enhanced TSHR-CART antitumor activity. This work represents a viable strategy to improve outcomes of patients with aggressive, metastatic thyroid cancers.

REFERENCES
Abstract 324 Figure 3  MEK inhibitors upregulate TSHR expression in ATC. H-score quantitation of TSHR expression (n=5 mice/group; * p<0.05, ** p <0.01).

Abstract 324 Figure 4  Sequential treatment of MEK/BRAF inhibition followed by TSHR-CART cell therapy demonstrates enhanced antitumor activity. Schema of treatment strategy (left panel). On day 0 or 7, NSG mice were engrafted with 5 mm3 ATC PDX. The day 0-innoculated mice, upon achieving tumor volume of ~100 mm3, were treated daily for 7 days with trametinib (1.5 mg/kg) plus dabrafenib (12.5 mg/kg) orally through ad libidum treated diet gel access to upregulate TSHR. On day 11, mice received 10 x 106 cells of either UTD or CART intravenously. Tumor volume of mice treated with UTD or TSHR-CART +/- trametinib + dabrafenib (right panel).