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SEA-TGT IS A NONFUCOSYLATED ANTIBODY WITH DISTINCT AND AMPLIFIED EFFECTOR FUNCTION ACTIVITY THAT LEVERAGES THE DEPENDENCIES OF ANTI-TIGIT ANTI-TUMOR ACTIVITY UPON FC γ R ENGAGEMENT

Alyson Smith*, Weiping Zeng, William Siegall, Bryan Grogan, Jane Haass, Amber Blackmarr, Robert Thurman, Scott Peterson, Shyra Gardai. *Seattle Genetics, Bothell, WA, USA*

Background TIGIT is an immunoregulatory receptor expressed on activated and memory T cells, T regulatory cells (Tregs), and NK cells. TIGIT binding to CD155 and CD112 on tumor cells drives an inhibitory signal resulting in decreased T cell functionality. TIGIT targeting has been reported to release these inhibitory signals, drive Treg depletion, augment CD8 T cell generation, and promote anti-tumor responses.

Methods To evaluate the impact of antibody backbone on anti-TIGIT action three distinct antibodies with differential backbone effector functions, wild type, Fc(gamma)R null (LALA), and Fc(gamma)R enhanced (nonfucosylated, SEA-TGT), were incorporated onto a human anti-TIGIT antibody and assessed. The nonfucosylated SEA-TGT backbone was distinct from the LALA and wild type backbone through increased binding to activating Fc γ RIIIa receptor while concomitantly decreasing binding to the inhibitory Fc(gamma)RIIb receptor.

Results Independent of backbone all TIGIT antibodies blocked ligand binding and restored CD226 signaling. The effector null backbone neither mediated Treg depletion nor naïve or memory CD8 T cell activation. However, the effector enhanced SEA-TGT significantly increased Treg depletion and activation of CD8 T cells over the comparator wild type anti-TIGIT antibody. The enhanced SEA-TGT also induced innate cell activation not seen with the other backbones. These in vitro results translated to curative in vivo anti-tumor activity in multiple syngeneic models as a single agent. Again, the effector null antibody was inactive in all models whereas the effector enhanced SEA-TGT drove curative responses beyond those seen with the standard wild type backbone. Increased activity correlated with a slight decrease in intra-tumoral Tregs and increases in CD8 memory T cells and innate cell activations. Anti-tumor response was associated with generation of long-term, antigen-specific immunity that resulted in complete tumor rejection upon tumor re-challenge.

Conclusions Collectively, these data indicate that modulation of CD8 T cell functionality is not solely through alterations in the TIGIT/CD226 signaling axis and that our nonfucosylated Fc γ R enhanced antibody uniquely activates both adaptive and innate arms of the immune system for maximal CD8 T cell responses. They also underscore the anti-tumor therapeutic potential of a nonfucosylated TIGIT targeting antibody (SEA-TGT) as a monotherapy agent and in combination with PD(L)1 agents. We have initiated a phase 1 trial testing the safety and activity of SEA-TGT in patients with advanced solid tumors and select lymphomas (NCT04254107).

Trial Registration NCT04254107

Ethics Approval Animals studies were approved by and conducted in accordance with Seattle Genetics Institutional Care and Use Committee protocol #SGE-029.

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FACTORS EVALUATED AS PREDICTORS OF EXCEPTIONAL RESPONSE TO PD-1 INHIBITORS IN PATIENTS WITH HEAD AND NECK SQUAMOUS CELL CANCER

Alexander Song*, Ron Ng, John Heller, Robin Petro, Ralph D'Agostino, Thomas Lycan, Mercedes Porosnicu. *Wake Forest School of Medicine, Winston Salem, NC, USA*

Background Immunotherapy has recently emerged as an alternative to traditional chemotherapy in the management of recurrent or metastatic head and neck squamous cell cancer (HNSCC). PD-1 inhibitors were approved for HNSCC in 2016 with ORR of 13–18% and CR of 4%.^{1, 2} Current research focuses on identifying predictors of response for better patient selection. We present HNSCC patients with exceptional response to PD-1 inhibitors in an attempt to highlight biomarkers that correlated with their remarkable response.

Methods We analyzed all cases of HNSCC treated with single agent PD-1 inhibitors in the last 4 years at Wake Forest Comprehensive Cancer Center. To identify exceptional responders, we followed the NIH Initiative definition: complete response to drug(s), where complete response is seen in less than 10% of patients receiving similar treatment or partial response lasting at least 6 months, where such response is seen in less than 10% of patients receiving similar treatment. We aimed to test all patients for PD-L1 expression, tumor genomics by Foundation Medicine platform and mutated circulating tumor DNA via Guardant 360 platform.

Results Based on the above criteria, 11 patients were identified as exceptional responders, 9 of whom had metastatic spread to lung, liver or bones. 7 patients were treated for more than one year, and all achieved CR. 3 patients were treated for less than one year, and all achieved major PR with possible CR to be confirmed with next scans. One patient with metastatic HNSCC achieved CR after just 3 administrations of PD-1 inhibitor and has been in CR for 3.5 years. 9 patients were tested for PD-L1 before starting immunotherapy, and all presented levels above 5% by TPS and above 10% by CPS. Interestingly, three patients older than 75 had the highest PD-L1: 75% by TPS and 100% by CPS in two patients. TMB was found moderate or high in all 8 patients tested before starting immunotherapy. TP53 was found mutated both in tumor and in blood in all but 2 of the 10 tested patients, one of whom is the only HPV positive patient in our series. MSI was stable in all patients.

Conclusions There are limited reports in the literature of exceptional responders to immunotherapy, particularly among HNSCC patients. High PD-L1 expression, moderate or high TMB and presence of mutated TP53 in both tumor and blood were present in almost all patients, recommending for further investigations as possible predictors of exceptional response to PD-1 inhibitors.

Ethics Approval The study was approved by Wake Forest University Institution's Ethics Board, approval number IRB00056249.

REFERENCES

1. T.Y. Seiwert, B. Burtness, R. Mehra, *et al.* Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. *Lancet Oncol* 2016;**17**(7):pp. 956–965.
2. Ferris RL, Blumenschein GJr, Fayette J, Guigay J, Colevas AD, Licitra L, *et al.* Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med* 2016;**375**:1856–67. 10.1056/NEJMoa1602252

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