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AGENT-797, A NATIVE ALLOGENEIC "OFF-THE-SHELF" INVARIANT NATURAL KILLER T (iNKT) CELL THERAPY PRODUCT IMPROVES EFFECTOR FUNCTIONS WITHIN THE TUMOR MICROENVIRONMENT

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Background T cell exhaustion is a common phenomenon that occurs in the tumor microenvironment (TME) due to prolonged exposure of T cells to tumor antigen. This is in part governed by the suppressive microenvironment created by myeloid cells. Immune checkpoint inhibitors have shown promising outcomes in clinical trials treating patients with solid cancer. However, not all patients with cancer respond to checkpoint therapy, demonstrating an unmet need to optimize the current approaches including cell therapies and combination strategies. We show here that agenT-797 can reinvigorate exhausted T-cells and differentially target myeloid cells

Methods We developed a multi-platform to evaluate interaction of agenT-797 with exhausted antigen-specific T cells and myeloid cells. Briefly, we transduced pan T cells with an NY-ESO-1 specific TCR and co-cultured them for multiple rounds with melanoma cell line, A375 that endogenously expresses HLA-A*02:01 and NY-ESO-1 antigen. Killing capacity, cytokine profile and phenotype of T cells were analyzed at each round of antigen exposure. We observed progressively reduced activity with each successive round. To assess whether addition of agenT-797 rescues functional impairment of partially exhausted T cells, we performed co-culture experiments of agenT-797 (or conditioned media) with T cells and A375 cells and monitored tumor cell killing and activation of T cells. In addition, we generated M1 and M2 macrophages and DCs and co-cultured them with agenT-797 to monitor activation and killing.

Results NY-ESO-1 specific T cells with progressive degree of exhaustion show reduced proliferation and IFN γ production along with increased TIGIT expression. Upon addition of agenT-797 into co-culture (or conditioned media), we observed increased IFN-g production and activation of CD8 T cells followed by restored cytotoxic capacity of partially exhausted T cells. agenT-797 was observed to selectively kill M2 macrophages over M1 macrophages, while increasing DC activation.

Conclusions iNKT cells are known to modulate the tumor microenvironment they are part of. Immune-infiltrated tumors contain T cells in different exhaustion states as well as suppressive myeloid cells. We addressed whether iNKT cells can reinvigorate such exhausted T cells and target suppressive macrophages. Our data demonstrates that agenT-797 can improve the function of partially exhausted T cells, selectively kill M2 macrophages, and enhance DC activation in addition to exhibiting their intrinsic natural anti-tumor activity. This highlights the potential of iNKT cells as a cell therapy platform and sheds more light on the mechanisms by which they can act.

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