

IL-2 COMBINATION WITH IMM-TAC OVERCOMES CD163 + TAM-LIKE M2 MACROPHAGE INHIBITION OF IMM-TAC-MEDIATED T CELL KILLING OF TUMOR CELLS

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Background ImmTAC molecules are bispecific fusion proteins consisting of an affinity-enhanced T cell receptor fused to an anti-CD3 effector that can redirect T cells to target cells. Tebentafusp, a gp100-directed ImmTAC, has demonstrated survival benefit in metastatic uveal melanoma [1]. We previously reported that a tumor microenvironment with a high immunosuppressive CD163+ tumor-associated macrophage (TAM): CD3 T cell ratio was associated with reduced benefit from tebentafusp [2]. Here, we explored whether IL-2 could potentiate T cells to overcome inhibition of ImmTAC-mediated killing by TAM-like M2 macrophages.

Methods Tumor biopsies from a Phase 2 trial of metastatic uveal melanoma HLA-A*02:01+ patients treated with tebentafusp (NCT02570308) were used to quantify CD163+ TAMs and CD3+ T cells by immunohistochemistry (N=107) and to measure gene expression by bulk RNAseq (N=70). Pro-inflammatory M1 and TAM-like M2 macrophages were generated in vitro from healthy donors (N=5) and their effect on ImmTAC-mediated T cell activation and tumor killing was assessed against THP-1 tumor cells. T cells were untreated or pre-treated for 4 days with commercially sourced IL-2 or IL-15.

Results In vitro, ImmTAC-mediated T cell killing of tumor cells was reduced by 85±5% in the presence of TAM-like M2 but not M1 macrophages. Consistent with this finding, below median CD163:CD3 ratio was associated with greater tumor shrinkage (TS) (odds ratio OR=2.9, p=0.014) and longer overall survival (OS) (hazard ratio HR=0.4, p=0.001) in tebentafusp-treated patients. We next explored in vitro whether the T cell activating cytokines IL-2 and IL-15 could overcome TAM-mediated inhibition of T cell redirection by ImmTAC. At clinically relevant doses, IL-2 but not IL-15 treatment resulted in dose dependent restoration of ImmTAC-mediated T cell killing of tumor cells in the presence of TAM-like M2 macrophages—60% and 83% restoration of killing at 50 and 150 U/ml of IL-2, respectively. Consistent with this observation, increased expression of IL2RB (HR 0.3, p<0.001) and IL2RG (HR 0.4, p=0.002), but not IL2RA (HR 0.8, p=0.5) in tumors was associated with longer OS on tebentafusp.

Conclusions Low CD163+ TAM to CD3 T cell ratio and high IL2RB/G expression in tumors at baseline were associated with longer OS and greater TS in tebentafusp-treated metastatic uveal melanoma patients in a Phase 2 trial. In vitro, TAM-like M2 macrophages suppressed ImmTAC-mediated T cell killing of tumor cells, an effect abrogated by IL-2. These observations provide strong rationale for combining IL-2 biased to IL2RB/G with ImmTAC molecules to enhance benefit in tumors with high levels of TAMs.

Trial Registration NCT02570308

REFERENCES

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2. Hassel JC, Benlahrech A, Stanhope S, et al. Abstract 1673: Uveal melanoma study patients with low CD163:CD3 ratio in tumor biopsy and low serum IL-6

showed enhanced tumor shrinkage (TS) and overall survival (OS) on tebentafusp. *Cancer Res.* 2021; 81 (13 Supplement) 1673.

Ethics Approval The Oxford A REC approved protocol 13/SC/0226 was used to obtain written consent for all blood donations and was fully approved by the National Research Ethics Committee South Central.

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