1196 GDF-15 NEUTRALIZING ANTIBODY VISUGROMAB INCREASES INTRATUMORAL IMMUNE CELL INFILTRATION TO SUPPORT BISPECIFIC T-CELL ENGAGERS

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Background GDF-15, a member of the TGF-beta superfamily, is a critical factor of feto-maternal tolerance, but also of local immune suppression at sites of cellular stress. Various solid tumor types secrete high levels of this immunosuppressive cytokine. In cancer patients, elevated GDF-15 serum levels correlate with poor prognosis and reduced overall survival.[1] Mechanistically GDF-15 interferes with LFA-1/ICAM-1 dependent immune cell extravasation and thus limits immune infiltration into GDF-15 expressing tumors. In line with immune infiltration as a prerequisite of checkpoint-inhibitor responses GDF-15 serum levels negatively correlate with the response to anti-PD-(L)1 CPI therapy.[2 3] Neutralization by clinical stage GDF-15 neutralizing antibody visugromab (CTL-002; GDFather-1/2 trial NCT04725474) restores responsiveness to anti-P(L)1 by increasing extravasation of immune cells into the tumor microenvironment.[2] To be active, bispecific T-cell engagers are dependent on infiltration of T-cells into the tumor tissue. Once bound to both T-cell and tumor cell, bispecifics retain T-cells at cancer cell sites. In this study we tested the synergy of visugromab with tebentafusp, a CD3-cell redirecting bispecific fusion protein for gp100$^+$ tumors, to enhance effector T-cell retention in the tumor.

Methods Specific binding and cytotoxic activity of tebentafusp was qualified by flow-cytometry and cytotoxicity assays with HLA-A2$^+$ gp100$^+$ human SK-MEL-5-melanoma cells, respectively. *In vivo* T-cell retention was tested in PBMC-humanized NOG mice, treated with tebentafusp[4] and isotype or a combination of tebentafusp and visugromab. After five days body weight, serum GDF-15, tumor size/weight and mouse and human immune cell infiltration were measured as a final read-out.

Results Tebentafusp bound gp100 on GDF-15 secreting HLA-A2$^+$ SK-MEL-5 melanoma cells and mediated tumor specific killing by T cells *in vitro*. *In vivo*, treatment with tebentafusp in combination with isotype resulted in a 4.3-fold increase in T-cell numbers in s.c. SK-MEL-5 tumors in PBMC-humanized NOG mice, while in combination with visugromab, a 15.3-fold increase was observed.

Conclusions GDF-15 is an inhibitor of immune infiltration, and its neutralization enhances effector cell presence in tumors. Bispecific T-cell engagers are dependent on proper effector cell infiltration into tumors to induce significant tumor cell killing. In a PD study combining tebentafusp with anti-GDF-15 antibody visugromab significantly increased the number of intratumoral T cells in mice. Increasing the number of effector cells in the tumor microenvironment is expected to have a direct positive impact on the anti-tumor activity of different bispecific T-cell engaging treatments.

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Ethics Approval This study was approved by EPO Berlin's Ethics Board; approval number E0023–23.

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