568 TUMOR-DERIVED GDF-15 PREVENTS THERAPY SUCCESS OF CHECKPOINT INHIBITORS BY BLOCKING T-LYMPHOCYTE RECRUITMENT

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Background Immune checkpoint blockade (ICB) can achieve durable responses in a subgroup of patients with metastatic cancer, only. Poor immune effector cell infiltration into the tumor microenvironment is a major obstacle to successful therapy. Growth and differentiation factor 15 (GDF-15) is a divergent member of the TGF-β superfamily and has been linked to feto-maternal tolerance, anorexia but recently also to potent local immunosuppression under physiologic and pathophysiologic conditions. GDF-15 is overexpressed in a wide variety of tumors and may be key factor produced by tumors to prevent effective immune cell infiltration into the tumor and to potently block checkpoint inhibitor activity.

Methods Effects of recombinant GDF-15 and a proprietary GDF-15 neutralizing antibody (CTL-002) on immune cell trafficking and activation were analyzed by adhesion and interaction assays and in melanoma-bearing humanized mouse models. The impact of GDF-15 overexpression was tested in subcutaneously implanted, GDF-15-transgenic MC38 cells. Additionally, patient GDF-15 serum levels were correlated with immune infiltration and OS in cutaneous melanoma. Associations between GDF-15 serum levels, response to PD-1-based ICB and corresponding OS were assessed in two independent cohorts of melanoma patients.

Results GDF-15 impairs adhesion of T and NK cells on activated endothelia. In HV18-MK bearing humanized mice, inhibition of GDF-15 strongly enhances infiltration of activated myeloid and lymphoid cells. In MC38 tumors, GDF-15 overexpression can abrogate tumor rejection upon anti-PD-1 therapy. 50% of the mice with GDF-15 overexpressing tumors were, however, rescued when anti-PD-1 was combined with anti-GDF-15 (CTL-002). Likewise, anti-GDF-15 improved responses to anti-CD40 + poly(I:C) in the same tumor model. Clinically, inverse correlations of GDF-15 levels with CD8+ T cell infiltration were shown for melanoma brain metastases. In two independent melanoma patient cohorts, low baseline serum GDF-15 levels predicted clinical response to anti-PD1 treatment and superior OS. Bivariate analysis including LDH indicates that GDF-15 is an independently predictor for poor survival in anti-PD-1 treated melanoma patients.

Conclusions Tumor-derived GDF-15 blocks the infiltration of immune effector cells into tumor tissues. Neutralizing GDF-15 with CTL-002 restores the ability of immune cells to extravasate blood vessels and enter the tumor microenvironment in vivo. GDF-15 thus represents a promising target for cancer immunotherapy. Antibodies against GDF-15 may support treatments with anti-PD-1 and other immunotherapeutic agents. A clinical trial combining anti-GDF-15 (CTL002) with anti-PD-1 (NCT04725474, submitted Abstract ID 15073) is ongoing.

Ethics Approval Use of patient samples for this study had been approved by the institutional ethics committee Tübingen (ethic vote 125/2015BO2). Use of surplus sera collected in the University of Zurich Hospital (USZ) Biobank during routine blood draws from consenting metastatic melanoma patients was performed according to IRB approval (KEK.Zh- 647/800) and followed the Declaration of Helsinki on Human Rights.

Consent All patients had given written informed consent to have clinical data recorded by the Central Malignant Melanoma Registry (CMMR) database.

http://dx.doi.org/10.1136/jitc-2021-SITC2021.568