ON203: A NEW ANTIBODY TARGETING THE OXIDIZED FORM OF MACROPHAGE MIGRATION INHIBITORY FACTOR (OXMIF) EXERTS ANTITUMORIGENIC ACTIVITY AND MODULATES THE TUMOR MICROENVIRONMENT

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Background Immunotherapy success in solid cancers is largely dependent on the tumor microenvironment (TME) and its modulation is central to improve clinical outcomes. One of the key players regulating the TME is the macrophage migration inhibitory factor (MIF), which contributes to an immunosuppressive environment. MIF induces polarization of macrophages to the M2 subtype, suppresses cytotoxic T cells and correlates with poor response to immune checkpoint therapy. MIF expression is associated with tumor aggressiveness, metastasis, and disease progression, but due to its ubiquitous nature is considered an elusive target for therapeutic intervention. In contrast, the disease-related structural isoform of MIF, termed oxMIF, is specifically present in solid tumor tissue. We now determined the antitumorigenic and TME-modifying potential of the new oxMIF-specific antibody ON203.

Methods In 3D tumoroids retaining an intact TME, which were isolated from colorectal carcinoma patients, tumor cell killing (high-content 3D computational bioimaging) and TME modulation (immune cell composition and activation, secretome analysis) induced by ON203 were analyzed. In vivo tumor penetration was assessed by infrared-labeled ON203 injected in tumor-bearing mice. Efficacy was assessed in human cancer cell-line (PC3) xenografted mice and ON203’s effects on tumor cell proliferation, vascularization and infiltrating immune cells were evaluated by immunohistochemistry.

Results Four out of five ON203-treated, freshly isolated tumoroids from colorectal carcinoma patients responded with significant tumor cell death. In the responding tumoroids a clear immunomodulatory effect on the tumor-associated immune cells was detected: ON203 activated NK and NKT cells (upregulation of Granzyme B and CD107a) and supported M1 polarization, correlating with reduced IL-10 levels in the secretome of ON203-responding tumoroids.

ON203 accumulated and retained in the tumor tissue in vivo and treatment of immunocompromised mice xenografted with human PC3 tumors led to significantly reduced tumor volumes. Tumor cell proliferation (assessed by Ki67 staining quantification) and tumor vessel density (CD31 staining quantification) were strongly decreased and currently ongoing analysis of tumor-infiltrating immune cells by immunohistochemistry and flow cytometry will provide further insights on the immunomodulatory therapeutic effects of ON203.

Conclusions The anti-oxMIF antibody ON203 demonstrated antitumorigenic effects by (i) reducing tumor cell proliferation, (ii) reducing angiogenesis and intravasation and (iii) by modulating the TME towards immunosupportive functions. In the upcoming clinical Phase 1 trial ON203’s safety, tolerability, pharmacokinetics, and pharmacodynamics in patients with solid tumors will be analyzed to evaluate its potential as a standalone or combinatorial therapy with immune checkpoint inhibitors, kinase inhibitors or antiangiogenic agents.