OMX-0407, A HIGHLY POTENT SIK3 INHIBITOR, SENSITIZES TUMOR CELLS TO APOPTOSIS AND ERADICATES TUMORS IN COMBINATION WITH PD-1 INHIBITION

Christina Hartl, Tillmann Michels, Ronny Milde, Vanessa Klein, Philipp Beckhove, Hannes Lofener, Stefan Bissinger*. Omx Therapeutics AG, Martinsried/Munich, Germany; RCI Center for Interventional Immunology, Regensburg, Germany

Background Interference with post-translational modifications such as methylation and acetylation of DNA and histones may enhance the intrinsic anti-tumor capacity of the immune system. Using the iOTarg genetic screening platform, salt-inducible kinase 3 (SIK3) was recently identified as a novel immune checkpoint that controls T cell-mediated apoptosis in tumor cells. SIK3, a serine/threonine kinase of the AMPK family, regulates pro-survival gene expression in tumor cells through epigenetic modulation of the NFκB-driven gene landscape via histone deacetylase 4 (HDAC4), causing the tumor to evade T cell-mediated killing.

Methods In turn, SIK3 knockout or knockdown abates downstream pro-survival signaling and sensitizes a panel of murine and human tumor cells to death receptor-mediated apoptosis. OMX-0407, an orally available, single-digit nanomolar inhibitor of SIK3 was shown to effectively reduce TNF-induced HDAC4 phosphorylation and downstream NFκB activity in a dose-dependent manner, thereby enhancing caspase-mediated apoptosis in murine and human tumor cell lines. Decreased intratumoral NFκB activity was demonstrated in vivo with an MC38 NFκB-luc reporter cell line.

Results Inhibition of the pro-tumorigenic NFκB pathway using OMX-0407 monotherapy translated into significant tumor growth inhibition (TGI) as well as prolonged survival in the highly infiltrated syngeneic murine colorectal carcinoma model MC38 (76% TGI). Moreover, OMX-0407 repolarized the tumor microenvironment (TME) by strongly reducing the number of regulatory T cells (T-regs) and M2-polarized macrophages in the tumor bed, while not affecting the peripheral T cell compartment. Thereby, exposure to OMX-0407 achieved a pronounced pro-inflammatory TME, characterized by a rise in activated cytotoxic T lymphocytes (CTL) and an increased CTL-to-T-reg ratio. Using the breast cancer mouse model EMT6, which represents an immune-excluded, cold tumor phenotype, we demonstrated that despite the minimal anti-tumor efficacy of OMX-0407 and anti-PD-1 monotherapy, respectively, upon combination treatment, both therapies synergize by combining apoptosis sensitization with a reduction in immunosuppressive TME and an increase in cytotoxic T cell activity. Combination treatment resulted in partial and complete tumor remissions in 60% of the animals, along with a significant prolongation of overall survival.

Conclusions In summary, OMX-0407, a first-in-class oral SIK3 inhibitor, demonstrates potent monotherapy efficacy in a pro-inflammatory tumor setting by reshaping the immune compartment and sensitizing tumor cells to death receptor-mediated apoptosis. The ability of OMX-0407 to remodel an immunosuppressed TME in a generally cold tumor setting, harbors great clinical potential for OMX-0407 combination therapy with anti-PD-1/PD-L1 immune checkpoint blockade, specifically in patients with high unmet medical need who are resistant to current immune checkpoint inhibitor monotherapy.