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A first-in-class SIK3 inhibitor, OMX-0370, effectively inhibits tumor growth in syngeneic tumor models, as single agent, by abolishing tumor resistance to immune-derived TNF

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SIK3 is an intracellular serine/threonine kinase belonging to the AMPK superfamily. We recently discovered a novel role of SIK3 in conferring TNF resistance to tumor cells. Resistance to TNF is an emerging mode of immune evasion in multiple solid tumors. In fact, while treating a broad panel of tumor cell lines with TNF we observed that almost 70% were either resistant or even proliferative in response to TNF. SIK3 knockout using CRISPR re-sensitized human PANC-1 and murine MC38 tumor cells to TNF-mediated death. Intratumoral SIK3 induces TNF resistance by retaining HDAC4 in the cytoplasm thus keeping the chromatin open and potentiating the TNF-driven pro-tumorigenic activity of NF-κB.

To translate these findings into the clinic, we have developed a potent (low nM range) inhibitor of SIK3, OMX-0370. Firstly, OMX-0370 exhibits dose-dependent inhibition of HDAC4 phosphorylation and nuclear NF-κB activity in response to TNF, thereby effectively neutralizing the SIK3-HDAC4-NF-κB axis. Consequently, treatment of human as well as murine tumor cells with OMX-0370 induces significant TNF-mediated apoptosis while sparing non-TNF treated cells. In mouse DMPK studies, OMX-0370 was found to be orally bioavailable with a favorable pharmacokinetic profile and was well tolerated at 100 mg/kg twice daily dosing in wild type C57BL/6 mice. Having shown a potent and favorable biochemical, functional as well as pharmacokinetic profile of the molecule, we next investigated the ability of OMX-0370 to inhibit the growth of established tumors in multiple syngeneic tumor models, including MC38, EMT6 and RENCA. Notably, OMX-0370 showed significant tumor growth inhibition as a single agent, which was found to be even superior to anti-PD-1 antibody treatment in RENCA and EMT-6 models. Immune profiling showed enhanced activation of intratumoral T cells, improved ratio of CTLs to Tregs and depletion of tumor-associated M2 macrophages, while no effect on peripheral leukocyte counts was observed. To monitor target engagement and pharmacodynamics of OMX-0370 *in vivo*, we developed a reporter MC38 cell line expressing luciferase under a NF-κB promotor. Using this reporter cell line, we could show that OMX-0370 inhibits TNF-induced NF-κB activation in a dose-dependent manner. Encouraged by the strong single-agent activity of OMX-0370 in solid tumor models, we have developed follow-on variants that exhibit higher potency as well as improved exposure *in vivo*.

In summary, we here report that OMX-0370, a first-in-class inhibitor of SIK3 kinase, is an active immunotherapeutic drug *in vivo* which effectively abolishes the TNF-driven NF-κB activity in tumors and re-sensitize them to TNF-induced apoptosis. OMX-0370 and its follow-on improved variants address the high unmet medical need of effective immunotherapeutic agents that neutralize clinically relevant and key orthogonal immune evasion axes in solid tumors as a monotherapy regimen.

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