Background The five-year survival rate for colorectal cancer (CRC) remains at 14% despite improvements in early detection and development of novel treatments, including immune checkpoint inhibitors (ICls). The immune landscape of CRC is heterogeneous and complex, posing challenges in treatment decision-making. Colorectal tumors presenting with microsatellite stable (MSS) or mismatch repair proficiency (MMRP) account for 85% of CRCs, which show little immune activity and respond poorly to ICls. New therapeutic strategies to overcome ICI resistance are needed to achieve a durable antitumor response in MSS/MMRP CRC. About 85% of CRCs exhibit chromosomal instability, which results in chromosome segregation errors and micronuclei formation. The latter releases dsDNA into the cytosol, stimulating a cyclic GMP-AMP synthase (cGAS)-Stimulator of Interferon Genes (STING)-dependent innate immune response. Preclinical studies have shown that activation of STING in the tumor microenvironment leads to induction of an interferon (IFN) response, activation of dendritic cells, and stimulation of T-cell responses. It is anticipated that activation of the innate immune response may help increase sensitivity to ICls. The therapeutic benefit from direct STING agonists is limited due to the widespread expression of STING in normal tissues. Ectonucleotide Pyrophosphatase/Phosphodiesterase-1 (ENPP1) is the only known direct negative regulator of the STING pathway that hydrolyzes 2′,3′-cGAMP, the direct activator of STING. Highest levels of 2′,3′-cGAMP can be found in tumors and recent evidence suggests that 2′,3′-cGAMP acts locally, as a paracrine immune transmitter. Therefore, inhibition of ENPP1 may produce superior outcomes by activating STING in the tumor microenvironment. We have developed SR-8541A, a highly selective and potent inhibitor of ENPP1. Additionally, we show that the inhibition of ENPP1 with SR-8541A enhances the effect of ICls in colorectal cancer models.

Methods In vivo studies were conducted using colorectal syngeneic mouse model (CT-26), which was engrafted subcutaneously and treated with SR-8541A ± α-CTLA4 ± α-PD-1 antibodies. Tumor growth and body weight were monitored over the course of the studies. IHC, RT-PCR, and mass spec analysis to identify adenosine levels were conducted on the tumors.

Results In vivo combination of SR-8541A with ICls exhibited a significant increase in overall efficacy compared to ICls alone. Tumors treated with the combination showed increased levels of CD3+ and CD8+ T-cell infiltration, increased levels of IFN response, and decreased levels of adenosine.

Conclusions Use of ENPP1 inhibition may sensitize colorectal cancers to immune checkpoint inhibition. We intend to explore this combination in the clinic.

REFERENCES