Background Increasing evidence suggests that myeloid populations are among the most sensitive to STimulator of Interferon Genes (STING) agonism and downstream interferon (IFN) production and could augment activity of α-PD-1, radiation, and other therapies. We present preclinical data with a murine surrogate ISAC, mTAK-500, designed to selectively deliver the STING agonist, TAK-676, to CCR2+ cells. This approach enables systemic delivery and is designed to achieve enhanced activity through prolonged exposure and selective targeting of CCR2+ cells.

Methods mTAK-500 was evaluated in preclinical in vitro and in vivo systems to characterize potency, exposure, mechanism, and antitumor activity alone and in combination with radiation or α-PD-1 treatment.

Results CCR2-mediated delivery of TAK-676 triggered dose-dependent activation of the STING signaling pathway and STING induced gene expression, as well as robust activation of innate and adaptive immune activity both in vitro and in vivo. Following systemic administration of mTAK-500 in preclinical studies, plasma exposure of total antibody and conjugated TAK-676 was observed beyond 24 hours. Characterization of exposure in the tumor revealed that systemic administration resulted in accumulation of mTAK-500 and liberation of TAK-676 in the tumor microenvironment (TME), however, TAK-676 was below limit of detection in plasma. Collectively, these observations demonstrate that CCR2-targeted delivery of TAK-676 prolongs exposure in the TME. In syngeneic mouse models, a transient decrease in peripheral monocytes along with dose-dependent activation of dendritic cells in the TME, lymph node, and periphery was observed. Further, mTAK-500 treatment caused increases in frequency, proliferation, and activation of peripheral CD8 T cells, ultimately resulting in accumulation and activation of CD8 T cells in the TME resulting in antitumor activity. The combination of 8 Gy radiation and mTAK-500 also resulted in increased frequency of CD8 tetramer specific T cells accompanied by an increase in antitumor activity observed in CT26 tumor bearing mice. In MC38 tumor bearing mice, treatment with a single dose of mTAK-500 treatment alone achieved strong antitumor activity, including a durable complete response (CR). Single agent α-PD-1 treatment also resulted in a 12.5% CR rate, however, when combined, mTAK-500 and α-PD-1 treatment achieved enhanced anti-tumor response with a 37.5% CR rate.

Conclusions Nonclinical antitumor activity and mechanistic insight have motivated design and clinical testing of TAK-500, a CCR2-targeted STING ISAC comprising the clinical stage STING agonist TAK-676 and a high-affinity antibody targeting human CCR2, as a single agent and in combination with pembrolizumab in adults with select locally advanced or metastatic solid tumors (NCT05070247).