1153 PRECLINICAL ACTIVITY OF C-C CHEMOKINE RECEPTOR 2 (CCR2)-TARGETED IMMUNE STIMULATING ANTIBODY CONJUGATE (ISAC), MOTIVATING CLINICAL TESTING OF TAK-500

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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).

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