

## REPROGRAMMING REGULATORY T CELLS (TREG) USING A MALT1 INHIBITOR FOR CANCER THERAPY

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**Background** MALT1 protease is a promising target in aggressive lymphomas<sup>1</sup>, and two phase 1 clinical trials in hematological cancers are ongoing (NCT03900598, NCT04876092). More recently, MALT1 protease inhibition was also shown to reprogram regulatory T cells (Treg) in solid tumors, causing them to lose their immunosuppressive function and secrete interferon-gamma (IFN).<sup>2</sup> Changes in Treg metabolism in the tumor microenvironment (TME) may account for their destabilization and selective susceptibility to reprogramming in tumor tissue.<sup>3 4 5</sup> While strong MALT1 inhibition can cause Treg depletion in blood and induce autoimmune toxicity,<sup>6</sup> a therapeutic window for a differentiated MALT1 inhibitor that reprograms destabilized Treg in the TME before affecting Treg in healthy tissue may exist.<sup>2</sup> MPT-0118 is an orally dosed MALT1 inhibitor developed to reprogram destabilized Treg in the TME without causing autoimmune symptoms. A Phase 1/1b dose-escalation and cohort-expansion clinical trial evaluating MPT-0118 is underway (NCT04859777).

**Methods** Human xenograft models of lymphoma were used to assess the direct activity of MPT-0118 on MALT1-dependent (but not MALT1-independent) hematologic tumors. Effects of MPT-0118 on solid tumors were determined in syngeneic cancer models. Human and mouse tumor tissues were evaluated for Treg reprogramming by *in situ* hybridization or flow cytometry. Patient-derived organotypic tumor spheroids were assessed for immune-mediated cell killing. Studies in rodents and dogs assessed pharmacokinetics (PK) and safety.

**Results** MPT-0118 was selective and effective in preventing growth of aggressive MALT1 protease-dependent lymphomas. Beyond direct activity on hematologic malignancies, MPT-0118 also increased anti-tumor immune responses as single-agent or in combination with anti-PD-1 in syngeneic tumor models that are otherwise unresponsive to immune checkpoint blockade (ICB). MPT-0118-treated syngeneic tumors showed an increase in IFN-secreting Treg, associated with decelerated tumor growth. PK studies reveal that MPT-0118 has a high volume of distribution, and effective inhibitor concentrations are reached in the murine tumors upon oral dosing. The drug candidate caused tumor-associated Treg to produce IFN without changing the frequency of Treg circulating in the blood. *Ex vivo*, MPT-0118 induced Treg reprogramming in tumors resected from patients with colorectal and endometrial cancers and cell killing in spheroids derived from patients with colorectal cancer.

**Conclusions** The MALT1 inhibitor MPT-0118 is a clinical candidate for treating MALT1-expressing lymphomas and Treg-infiltrated solid tumors. MPT-0118 exploits the therapeutic opportunity presented by destabilized Treg in the TME. Treg reprogramming represents a novel strategy with the potential to improve responses to ICB therapy in a broad range of solid tumors.

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