

Immunology

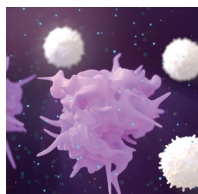
Major finding: Inhibition of class IIa HDACs with TMP195 promotes a macrophage-dependent reduction in tumor burden.

Approach: TMP195 alters the tumor microenvironment to promote antitumor macrophage recruitment and differentiation.

Impact: Targeting class IIa HDACs may enhance the efficacy of chemotherapy and checkpoint blockade.

TARGETING CLASS IIa HDACs MAY SUPPRESS BREAST TUMORS AND METASTASES

Tumor-associated macrophages (TAM) are often protumorigenic, and strategies have emerged to promote their antitumor effects. Selective inhibition of class IIa histone deacetylases (HDAC) with the small-molecule inhibitor TMP195 induces changes in monocyte gene expression without affecting lymphocyte gene expression, and promotes a type 1 proinflammatory monocyte phenotype. Thus, Guerriero and colleagues tested the hypothesis that class IIa HDAC inhibition promotes an antitumor innate immune response using a transgenic mouse model of luminal B-type mammary carcinoma in which CSF-1 and macrophages control late-stage carcinogenesis and pulmonary metastasis. Indeed, TMP195 induced a macrophage-dependent decrease in tumor burden and pulmonary metastasis. TMP195 promoted expression of genes associated with an activated immune cell signature, increased the proportion of CD11b⁺ cells and mature macrophages, reduced the proportion of protumor TAMs, induced the appearance of cells resembling highly phagocytic tingible body macrophages, and increased the proportion of activated cytotoxic (granzyme B positive) T lymphocytes in tumors. Altogether, these findings suggest that class II HDAC inhibition



enhances the phagocytic and immunostimulatory functions of macrophages, promoting an antitumor phenotype that boosts activation of cytotoxic T lymphocytes. *In vivo*, depletion of myeloid cells or macrophages reduced the antitumor activity of TMP195, indicating that activated macrophages are required for TMP195-mediated tumor suppression. Further, IFN γ was required to alter the tumor microenvironment and activate the TMP195-mediated antitumor immune response. In the mouse model of breast cancer, TMP195 enhanced the efficacy and durability of chemotherapy and anti-PD1 immunotherapy. Collectively, these findings demonstrate that inhibition of class IIa HDACs can promote tumor suppression by enhancing the antitumor activity of macrophages, and suggest that targeting class IIa HDACs may potentially enhance the efficacy of standard therapies in patients with breast cancer. ■

Guerriero JL, Sotayo A, Ponichtera HE, Castrillon JA, Pourzia AL, Schad S, et al. Class IIa HDAC inhibition reduces breast tumours and metastases through anti-tumour macrophages. *Nature* 2017;543:428–32.

Clinical Trials

Major finding: The MDM2 inhibitor MK-8242 is tolerable in patients with liposarcoma and other advanced solid tumors.

Concept: MK-8242 increases expression of the p53 target gene *PHLDA3*, suggesting that it activates p53.

Impact: MK-8242 may activate p53 to produce antitumor activity in patients with TP53-wild-type tumors.

MK-8242 IS ACTIVE IN PATIENTS WITH p53 WILD-TYPE ADVANCED SOLID TUMORS

MDM2, a negative regulator of p53, is amplified in multiple tumor types, including a large majority of liposarcomas. Thus, targeting MDM2 is a potential therapeutic strategy for p53 activation. MK-8242 is a potent, orally bioavailable, small-molecule inhibitor of the MDM2–p53 interaction. In a phase I dose-ranging study, Wagner and colleagues evaluated MK-8242 in 47 patients with TP53-wild-type advanced solid tumors, 27 of whom had liposarcoma. The primary endpoints were to identify dose-limiting toxicities and establish the recommended phase II dose, and secondary endpoints included determination of the objective radiologic response rate (ORR). In total, 46 of 47 (98%) patients had at least one drug-related adverse event, including 4 (8.5%) who experienced serious drug-related adverse events, and 12 patients (26%) discontinued treatment as a result of adverse events. In patients receiving 300 mg, 400 mg, or 500 mg MK-8242, expression of the p53 target gene *PHLDA3* increased, suggesting that MK-8242 treatment results in p53 activation. The recommended

phase II dose was determined to be 400 mg. The ORR was 6.4%, with an ORR of 11.1% in patients with liposarcoma. Three patients achieved partial responses and 31 showed stable disease. The median progression-free survival was 3.4 months overall and 7.8 months in patients with liposarcoma. Taken together, the results of this phase I trial indicate that MK-8242 has an acceptable safety profile at the determined recommended dose, and may have antitumor activity in patients with p53-wild-type tumors, particularly those with liposarcoma. These findings support further investigation of MDM2 inhibitors including MK-8242 as a strategy to activate or reactivate p53, alone or in combination with conventional chemotherapy for the treatment of cancer. ■

Wagner AJ, Banerji U, Mahipal A, Somaiah N, Hirsch H, Fancourt C, et al. Phase I trial of the human double minute 2 inhibitor MK-8242 in patients with advanced solid tumors. *J Clin Oncol* 2017 Feb 27 [Epub ahead of print].