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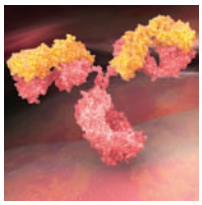
Clinical Trials

Major finding: Anti–PD-1 therapy with pembrolizumab achieved responses in 18% of patients with soft-tissue sarcoma.

Approach: The SARC028 open-label, phase II trial evaluated pembrolizumab in 84 patients with advanced sarcoma.

Impact: Pembrolizumab warrants further investigation in undifferentiated pleomorphic sarcoma and liposarcoma.

PEMBROLIZUMAB MAY BE BENEFICIAL IN A SUBSET OF SOFT-TISSUE SARCOMAS



Treatment options are limited for patients with advanced sarcomas. Immune checkpoint blockade therapies, including the anti–PD-1 antibody pembrolizumab, have had success in a number of tumor types, but have not been well studied for the treatment of sarcoma. In the SARC028, two-cohort, open-label, phase II trial, Tawbi and colleagues evaluated the safety and efficacy of pembrolizumab in patients with advanced soft-tissue or bone sarcoma. A total of 84 patients were enrolled and treated with pembrolizumab. The primary endpoint was objective response rate. Secondary endpoints included incidence of adverse events, progression-free survival, and overall survival. There were 40 evaluable patients in each cohort. Overall, 7 of 40 (18%) patients with soft-tissue sarcoma had an objective response, including 4 of 10 (40%) patients with undifferentiated pleomorphic sarcoma, 2 of 10 (20%) patients with liposarcoma, and 1 of 10 (10%) patients with synovial sarcoma. None of the 10 patients with leiomyosarcoma achieved an objective response. The median progression-free survival for patients with soft-tissue sarcoma was 18 weeks, the 12-week progression-free survival 55%, the median overall survival was 49 weeks, and the median duration of response was 33 weeks. Of the 40 patients with bone sarcoma, 2 (5%) had an objective response, 1 of 22 patients (5%) with osteosarcoma and 1 of 5 patients (20%) with chondrosarcoma. None of the 13 patients with Ewing sarcoma experienced an objective response. The median progression-free survival was 8 weeks, median overall survival was 52 weeks, and median duration of response was 43 weeks. The safety profile was consistent with what had previously been reported for pembrolizumab. Collectively, the results of the SARC028 trial suggest that immune checkpoint blockade may be effective in a subset of patients with soft-tissue sarcoma, and further clinical studies are ongoing in patients with undifferentiated pleomorphic sarcoma and dedifferentiated liposarcoma. ■

Tawbi HA, Burgess M, Bolejack V, Van Tine BA, Schuetze SM, Hu J, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicenter, two-cohort, single-arm, open-label, phase 2 trial. Lancet Oncol 2017;18:1493–501.

Leukemia

Major finding: The small-molecule BAX activator BTSA1 promotes apoptosis of AML cells *in vitro* and *in vivo*.

Mechanism: BTSA1 binds to the N-terminal BAX activation site to promote potent and selective BAX activation.

Impact: Pharmacologic BAX activation may promote apoptosis in AML cells without affecting normal hematopoiesis.

BTSA1 ACTIVATES BAX TO PROMOTE APOPTOSIS IN ACUTE MYELOID LEUKEMIA

BAX is a proapoptotic BCL2 family protein that can be suppressed by overexpression of antiapoptotic BCL2 proteins to promote tumorigenesis and resistance to therapy in cancer. Clinical inhibitors of antiapoptotic BCL2 proteins are available, including venetoclax, and can promote BAX/BAK-mediated apoptosis, but they have limited efficacy in tumors that overexpress additional antiapoptotic proteins. Most cancer cells express BAX in an inactive conformation or suppressed by antiapoptotic proteins, suggesting the possibility for therapeutic activation of BAX to promote apoptosis in cancer. In order to develop a BAX activating compound, Reyna and colleagues performed structure-based drug design and chemical synthesis combined with a competitive fluorescence polarization assay to screen compounds for binding to the N-terminal BAX activation site (trigger site). The lead compound, BAX Trigger Site Activator 1 (BTSA1), exhibited potent and selective BAX activation, inducing a conformational change to transform inactive cytosolic BAX to its active oligomeric form capable of triggering apoptosis. BTSA1 treatment induced apoptosis in human acute myeloid leukemia (AML) cell lines, but not in BAX-deficient cells. Further, BTSA1 induced apoptosis of primary AML blast cells and preleukemic stem cells, which expressed high levels of BAX, in a dose-dependent manner, but did not affect healthy hematopoietic stem and progenitor cells. BTSA1 also synergized with venetoclax to promote AML cell apoptosis *in vitro*. *In vivo*, BTSA1 was well tolerated, having no effect on normal hematopoiesis, orally bioavailable, and had excellent pharmacokinetics. BTSA1 treatment induced apoptosis to suppress the growth of human AML xenografts. The identification of BTSA1 as a potent and selective BAX activator suggests the feasibility of therapeutically activating BAX to promote cancer cell apoptosis, and BTSA1 exhibited antileukemic activity both *in vitro* and *in vivo*. ■

Reyna DE, Garner TP, Lopez A, Kopp F, Choudhary GS, Sridharan A, et al. Direct activation of BAX by BTSA1 overcomes apoptosis resistance in acute myeloid leukemia. Cancer Cell 2017;32:490–505.e10.

AACR American Association for Cancer Research

CANCER DISCOVERY

BTSA1 Activates BAX to Promote Apoptosis in Acute Myeloid Leukemia

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