TAK-243 is a potent and selective ubiquitin-like modifier activating enzyme 1 (UBA1) inhibitor. IC50 & Target: UBA1[1] In Vitro: TAK-243 (MLN7243) selectively kills a subset of cutaneous squamous cell carcinoma (cSCC) lines. squamous cell carcinoma transplant (SCCT) and SCCRDEBMet cells are the most susceptible to continuous treatment with TAK-243. SCCIC1Met cells are also selectively killed by an extended exposure to TAK-243. Death in SCCRDEBMet cells displays the greatest sensitivity to a pulse of TAK-243.

MLN7243 can reduce the cellular level of ubiquitin conjugates. TAK-243 decreases UBA1 and UBA6 thioesters and thioesters of the UBA6 specific E2 UBE2Z/USE1[1]. TAK-243 displays preferential activity towards acute myeloid leukemia (AML) cells over normal hematopoietic cells. TAK-243 reduces growth and viability of human AML cell lines (OCI-AML2, TEX, U937 and NB4) in a concentration- and time-dependent manner with IC50’s ranging from 15-40 nM after treatment for 48 hours[2].

In Vivo: TAK-243 significantly delays tumor growth in mice (T/C=0.02) with no toxicity as evidenced by no changes in mouse body weight, serum chemistry, or organ histology. TAK-243 reduces primary AML tumor burden in both tested samples without toxicity[2].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: [1]Normal keratinocytes (normal human keratinocytes (NHK) and recessive dystrophic epidermolysis bullosa keratinocytes (RDEBK)) and cSCC cell lines are seeded into 96 well plates and live cell number and cell death are analysed with an IncuCyte ZOOM real-time imager using the CellTox Green Cytotoxicity Assay. Relative EC50 values are determined using GraphPad Prism. For clonogenic assays cells are seeded into six well plates. Inhibitors (e.g., TAK-243; 0.01, 0.1, 1, and 10 μM) are added for the indicated times and then cells are maintained in drug-free medium for up to 2 weeks to allow colony formation. Colonies are fixed in 10% methanol, 10% acetic acid and stained with crystal violet[1].

The preclinical efficacy and toxicity of TAK-243 are assessed in mouse models of AML. OCI-AML2 cells are injected subcutaneously (sc) into SCID mice, and when tumors are palpable, mice are treated with TAK-243 (20 mg/kg sc twice weekly). As an additional model, primary AML cells from 2 patients are injected into the femurs of NOD-SCID mice. Two weeks after injection, mice are treated with TAK-243 (20 mg/kg sc twice weekly). After 3 weeks of treatment, mice ae sacrificed, and AML engraftment in the non-injected femur is measured by flow cytometry[2].

CAIndexNames:

SMILES:
Caution: Product has not been fully validated for medical applications. For research use only.

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