Cleveland Clinic Innovations

TET inhibitor treatment for myelodysplastic syndromes

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PRODUCT

Potent small molecule inhibitor of TET dioxygenase

INDICATION

Treatment for myelodysplastic syndromes (MDS), acute myeloid leukemia (AML), and clonal hematopoiesis of indeterminate potential (CHIP)

VALUE PROPOSITION

Selectively kills TET deficient ($TET2^{MT}$) stem cells while providing proliferative advantage to non-mutated stem cells

DEVELOPMENT STAGE

Preclinical lead series with nanomole potency and therapeutic index

INTELLECTUAL PROPERTY

US 11,865,104
EP 18821839
Additional filings planned

RELATED PUBLICATIONS

Guan, Yihong et al. “A Therapeutic Strategy for Preferential Targeting of TET2 Mutant and TET-dioxygenase Deficient Cells in Myeloid Neoplasms.” Blood Cancer Discovery Vol. 2,2 (2021): 146-161. PMID: 33681816

Gurnari, Carmelo et al. “TET2 mutations as a part of DNA dioxygenase deficiency in myelodysplastic syndromes.” Blood advances vol. 6,1 (2022): 100-107. PMID: 34768283

CONTACT INFORMATION

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UNMET NEED

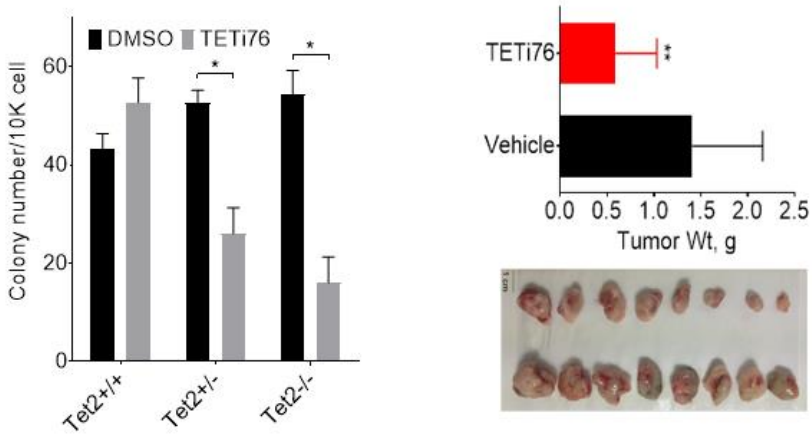
Myelodysplastic syndrome (MDS) represents a group of cancers in which immature blood cells in the bone marrow fail to mature properly. Approximately 30% of patients with MDS progress to acute myeloid leukemia (AML). Standard of care treatment for MDS is limited to blood transfusions, small molecule drugs that enhance blood cell production, and bone marrow transplants – none of which are curative.

Ten-Eleven-Translocation Methylcytosine Dioxygenase 2 (TET2) is part of a family of proteins that play a major role in tumor suppression. TET Dioxygenases act as the functional gatekeepers of efficient and accurate transcription, determining differentiation and cellular homeostasis.

Loss of TET2 is clonal and leads to neoplastic evolution by perturbing cell lineage fate, promoting proliferation and myeloid neoplasia progression. TET2 is one of the most commonly mutated genes in adult myeloid malignancies, including 30% of cases of MDS, 20% of myeloproliferative neoplasms (MPNs), 17% of de novo AMLs, 30% of secondary AMLs and >50% of chronic myelomonocytic leukemias. TET2 mutations ($TET2^{MT}$) are associated with shortened time period to progression to AML and inferior survival rates. $TET2^{MT}$ as founder lesions constitute a suitable treatment target with decreased potential of recurrence.

SOLUTION

The $TET2^{MT}$ cells are highly dependent on residual TET- activity (provided by TET1 and TET3) for survival and proliferation. Inhibition of residual TET activity pushes cells with $TET2^{MT}$ lineage into cell death, sparing normal hematopoietic stem cells (HSC). Cleveland Clinic’s novel TET-inhibitor selectively kills TET deficient $TET2^{MT}$ ‘bad’ stem cells while providing proliferative advantage to ‘good’ stem cells. Efficacy was demonstrated in a human TET2−/− leukemia cell line xenograft model. Oral treatment significantly reduced tumor burden compared with vehicle treated mice.



TET-inhibition demonstrates effective reduction in cell proliferation of TET deficient cells specifically, sparing normal cells, and significantly reduces myeloid tumor size in vivo