369 DHODH Inhibitors for Treatment of Hematological Malignancies

Asset Overview

Product Type	Small molecule
Indication	Hematological malignancies including acute myeloid leukemia (AML)
Current Stage	Lead optimization/ Pre-clinical
Target(MoA)	Dihydroorotate dehydrogenase (DHODH)
Brief Description	DHODH is a rate-limiting enzyme in de novo pyrimidine synthesis. Rapidly dividing cancer cells are therefore sensitive to blockade of this pathway. New research has shown DHODH inhibition can induce differentiation in AML cell lines, translating to increased survival in animal models. There is also evidence that DHODH inhibitors can produce cytotoxic effects through p53 upregulation and mitochondrial effects.
Organization	The Ohio State university

Differentiation

□ **Targeting DHODH to treat AML**

- AML patients are usually given induction chemotherapy with cytarabine and an anthracycline (daunorubicin). its success has been limited except in specific genetic subtypes of AML. The five-year survival (Hematopoietic stem cell transplantation) remains less than 30%
- **Brequinar** (DHODH inhibitor, by Bristol-Myers Squibb) had been in phase II clinical trials for the treatment of cancer and transplant rejection. Phase-I/II clinical trials in Acute myeloid leukaemia (Second-line therapy or greater) in USA (PO) (NCT03760666). Brequinar was inactive in tumors evaluated possibly because of (local) high uridine levels in the solid tumor

□ **More potent than Brequinar in AML cell lines**

- Differential growth inhibition compared to Brequinar in murine AML models with defined genetic phenotype. Patent protection for chemical composition is done
- The Biochemical IC50 of Compound 1 is 43 nM
- Recent studies have shown that DHODH is a key enzyme in the metabolic pathway in cancer cells, and its inhibition reduced the viability of cancer cells in vitro and strongly suppressed tumor growth in human patient-derived xenograft (PDX) models

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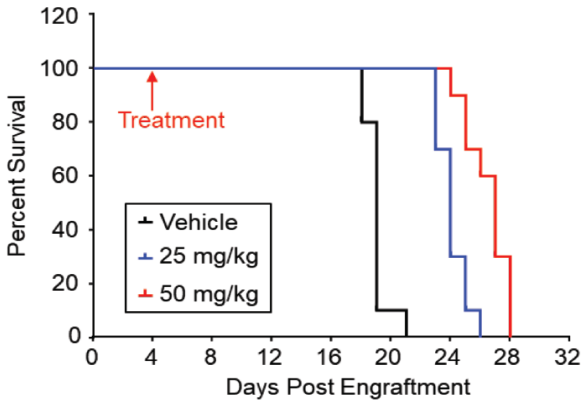
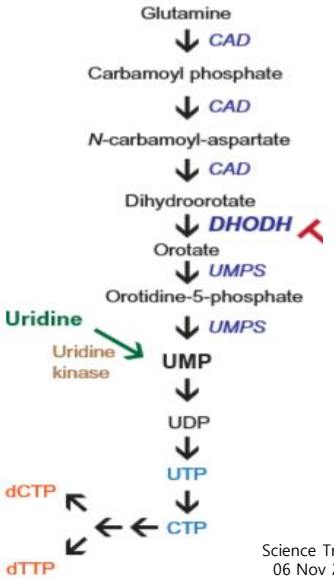
Key Data

Oral administration of Compound 1 increases survival in mice



Daily Oral Administration of Compound 1 Produces Dose Dependent Increased Survival in Disseminated MOLM-13 Murine Model
Vehicle vs. 25 and 50 mg/kg of Compound 1; each $p < 0.001$. ↑ = treatment start.



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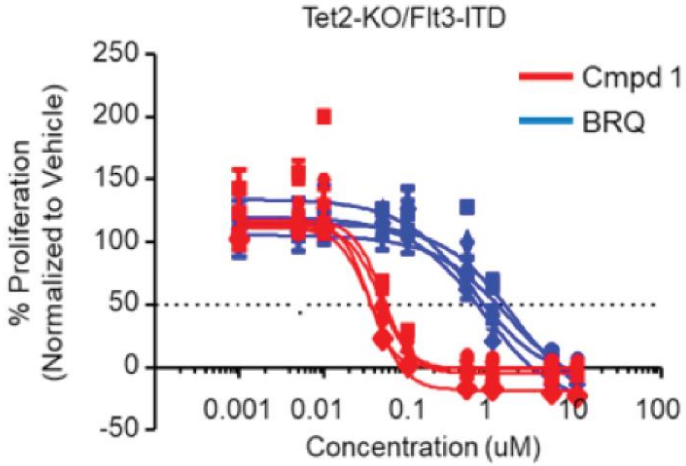
The growth inhibition of Compound 1 compared to Brequinar

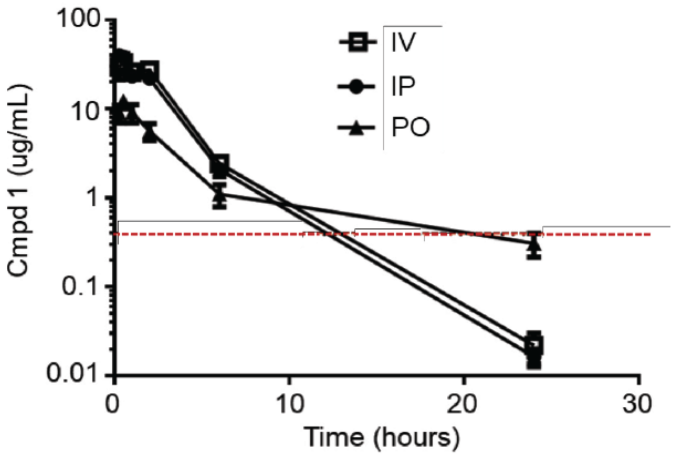
More potent growth inhibition compared to Brequinar:
Murine splenocytes isolated from leukemic Tet2-KO/Flt3-ITD mice (N=7) were treated *ex vivo* with Compound 1 or Brequinar (dose range 0 – 10 uM). Cell growth was determined at 96 hours relative to the vehicle (DMSO) control using an MTS assay.



Advantages

- More potent than Brequinar in AML cell lines (Brequinar is in early clinical trials for AML.)
- Differential growth inhibition compared to Brequinar in murine AML models with defined genetic phenotype.
- Patent protection for chemical composition

Oral PK (Pharmacokinetic) analysis result



Favorable Oral PK: Single dose (10 mg/kg) in WT B6 mice (N=4 per route). Plasma was sampled by repeat blood draw.

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Intellectual Property

Patent No.	
Application Date	
Status	
Country	

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