376 HOSU-3, DHODH Inhibitor for Acute Myeloid Leukemia

Asset Overview

Product Type	Small Molecule
Indication	Oncology, Hematological diseases
Current Stage	Lead identification / optimization
Target(MoA)	Dihydroorotate dehydrogenase (DHODH) Inhibitor
Brief Description	• Novel DHODH inhibitors developed • HOSU-3 induces cell death and differentiation primary AML blasts • HOSU-3 exhibits sustained, dose linear oral bioavailability in mice • In vitro ADME was completed with no major concerns • Established in vivo efficacy of HOSU-3 in a xenograft model • Next milestones: additional assessment of in vivo efficacy & new analogs development
Organization	The Ohio State University

Differentiation

□ **DHODH as a therapeutic target in cancer**

- DHODH is critical for de novo pyrimidine biosynthesis and for inducing AML differentiation.
- One hallmark of AML is that the leukemic blast is arrested at an early stage of differentiation.
- Efforts to identify new therapeutic targets to overcome myeloid differentiation blockade have been largely unsuccessful. Small molecule inhibitors of mutant isocitrate dehydrogenase (IDH)2 (IDH2) (Wang et al., 2013) or IDH1 (Okoye-Okafor et al., 2015) may be capable of inducing cellular differentiation among that subset (15%) of patients with IDH1/2 mutations. However, the remainder of AML cases involve complex and heterogeneous combinations of chromosomal alterations and gene mutations, highlighting the difficulty in developing mutation-specific therapies.
- Inhibiting DHODH with brequinar(BRQ) has been shown to induce differentiation in AML and prolong survival in AML animal models
- Brequinar(BRQ) was unsuccessful clinical development in solid tumor cancers.
- Targeting DHODH in AML represents a promising new treatment strategy with the potential to have a broad impact.

□ **DHODH inhibitor pipelines**

- Teriflunomide (Aubagio, Sanofi): Marketed for multiple sclerosis
- ASLAN-003 (Aslan): Phase II for AML, 1st line & 2nd line therapy (Phase I for multiple sclerosis & RA, now inactive), preclinical for HCC and TNBC
- Brequinar (Clear Creek Bio): Phase II for refractory and relapsed AML
- Olorofim (F-901318, F2G): Phase II for infectious disease
- Vidofludimus calcium (IMU-838, Immunic): Phase II for Crohn's disease, ulcerative colitis
- AG-636 (Agios): Phase 1 for refractory AML etc.
- BAY-2402234 (Bayer): Phase I for relapsed or refractory AML, myelodysplastic syndrome, diffuse large B-cell lymphoma and colorectal cancer and relapsed or refractory chronic myelomonocytic leukemia
- RP7214 (Rhizen): Preclinical for AML, single-agent activity in AML cell lines and anti-tumor activities in both tumor size and tumor weight in MV-4-11 human leukemia xenograft model. potentiated the activity of gilteritinib in reducing cell growth, induction of apoptosis (poster at 2019 AACR-NCI-EORTC)

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Key Data

HOSU-3 is a potent inhibitor of DHODH and has anti-proliferative activity in AML

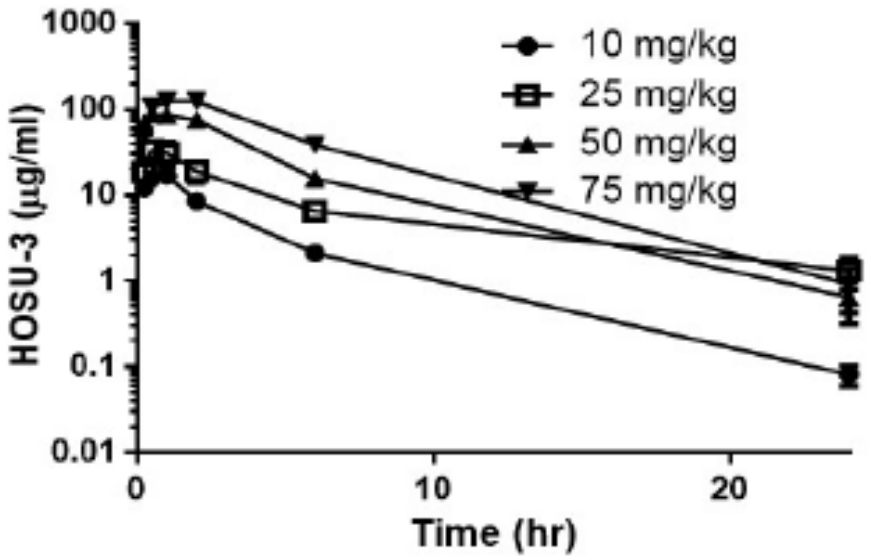
DHODH inhibition		
Compound	% inhibition	IC50, uM
HOSU-3	97	0.043 (0.039 - 0.047)
HOSU-5	95	0.099 (0.092 - 0.11)
HOSU-6	99	0.076 (0.07 - 0.083)
HOSU-17	8	ND*

Cell free enzymatic assay for several derivatives indicate potent DHODH inhibitory activity.

	IC50 (uM) at 96 hours				
Compound	MOLM-13	MV4-11	THP1	HL-60	OCI-AML3
HOSU-3	0.4	0.67	1.1	0.28	0.61
HOSU-4	5.38	13.1	17.82	5.94	6.19
HOSU-5	3.02	6.96	7.84	20.9	3.37
HOSU-6	6.91	6.48	10.39	3	6.25
HOSU-8	6.76	7.54	11.56	3.57	4.99
HOSU-9	6.98	8.17	13.45	3.3	3.58
HOSU-14	8.63	13.99	21.4	9.48	11.2
HOSU-16	3.42	6.23	6.7	1.69	2.9
HOSU-18	6.76	6.86	9.34	2.4	4.01
BRQ.Na	0.48	0.49	1	0.23	0.4
ATRA	3.06				0.09

IC50 values for the 9 most highly active derivatives based on MTS assays in AML cell lines.

Dose linear oral bioavailability in mice



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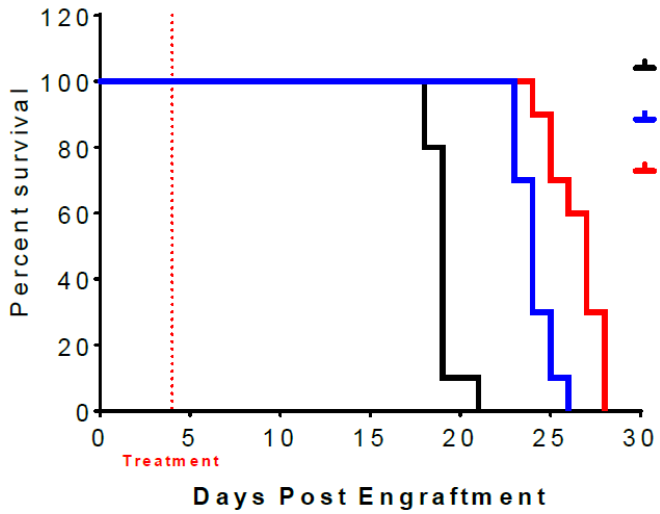
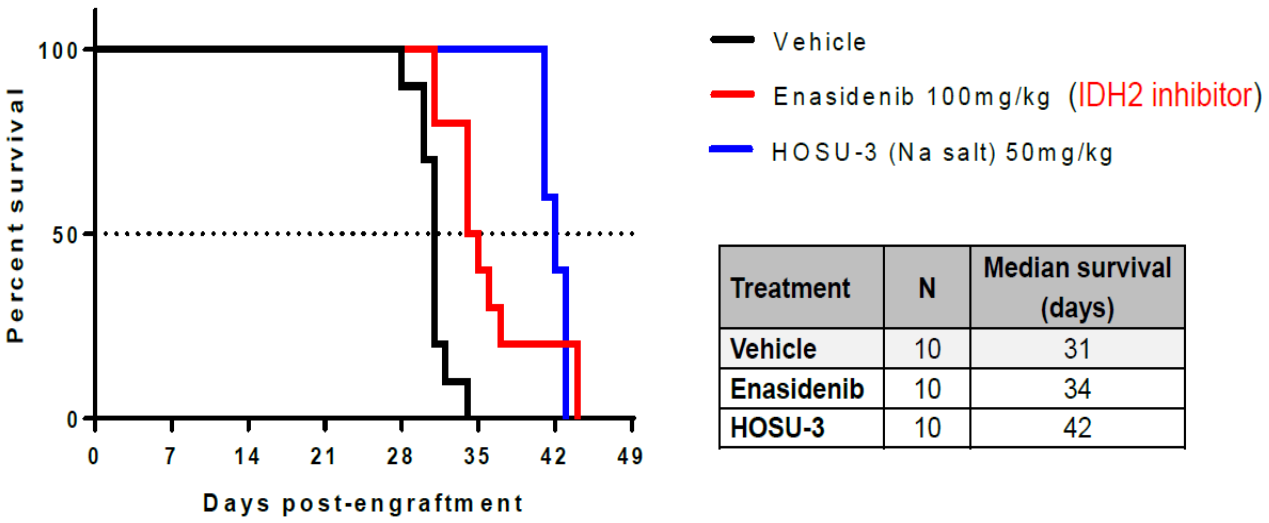
In vivo efficacy of HOSU-3 in MOLM13 disseminated xenograft mouse model



Group	N	Median survival time (days)
Vehicle	10	19
25mg/kg HOSU3 QD PO	10	24
50mg/kg HOSU3 QD PO	10	27

In vivo efficacy of HOSU-3 in syngeneic mouse model IDH2^{R140Q}/FLT2-ITD murine leukemia



Treatment	N	Median survival (days)
Vehicle	10	31
Enasidenib	10	34
HOSU-3	10	42

Treatment began 7 days post-engraftment (daily oral gavage)

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Intellectual Property

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