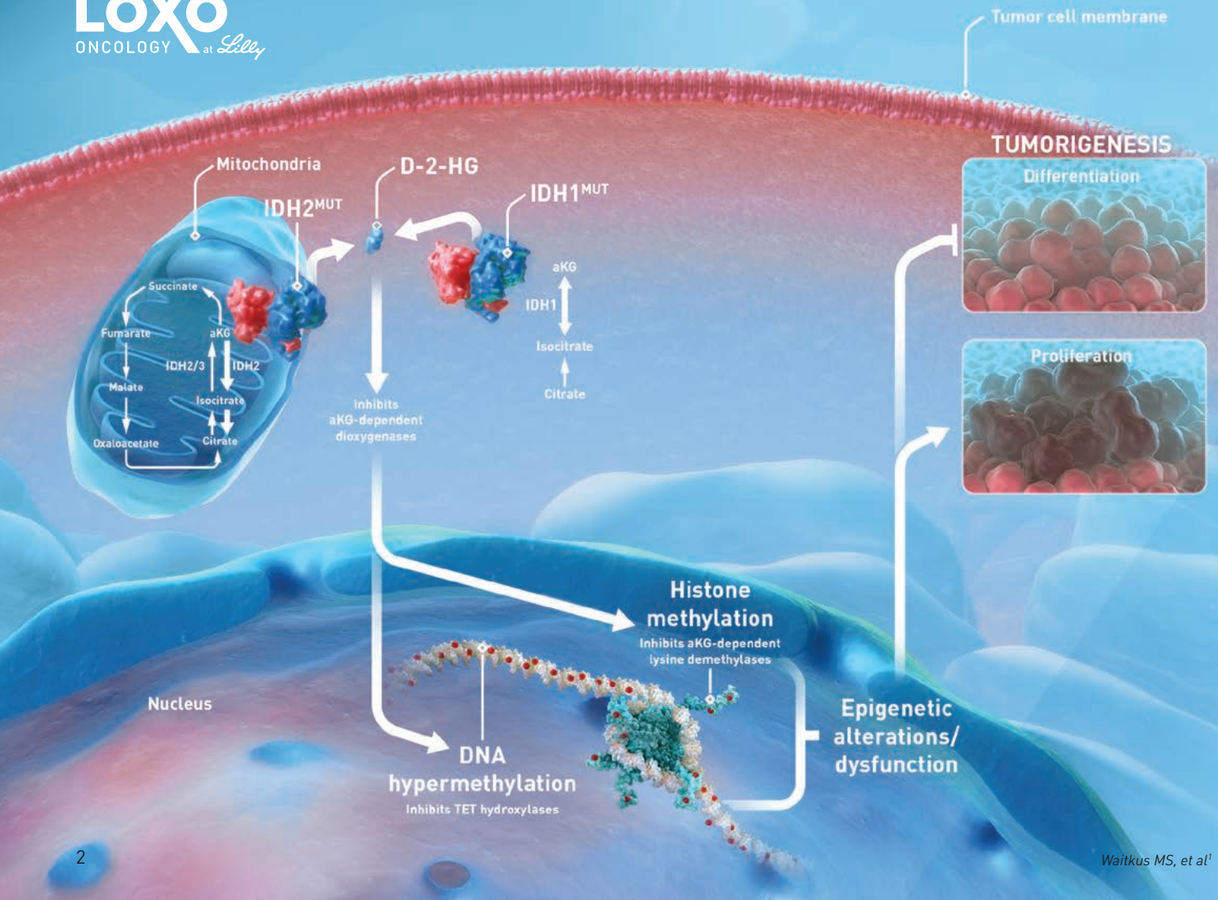

LOXO
ONCOLOGY at Lilly
LY3410738
IDH1 INHIBITOR



Waitkus MS, et al[1]

Target

The enzyme isocitrate dehydrogenase (IDH1) is mutated in a variety of cancers, including acute myeloid leukemia (AML), cholangiocarcinoma, chondrosarcoma, and glioma.[2-5] These mutations are typically somatic gain-of-function mutations located in arginine 132 (R132) that grant IDH1 the ability to produce 2-hydroxyglutarate (2-HG).[6] 2-HG is an oncometabolite that promotes tumor development by inhibiting enzymes that maintain normal DNA and histone methylation, leading to hypermethylation associated with transcriptional dysregulation.[6,7] As a result, IDH1-mutated cells become blocked in a progenitor-like state and contribute to tumor development both directly through cellular self-renewal and indirectly through cooperation with other oncogenic drivers.[7]

Molecule

LY3410738 is a potent, selective, and covalent inhibitor of mutant *IDH1* that has been shown in vitro and in vivo to rapidly inactivate mutant *IDH1* and inhibit 2-HG production without impacting wild-type *IDH1*.[8]

Clinical Development

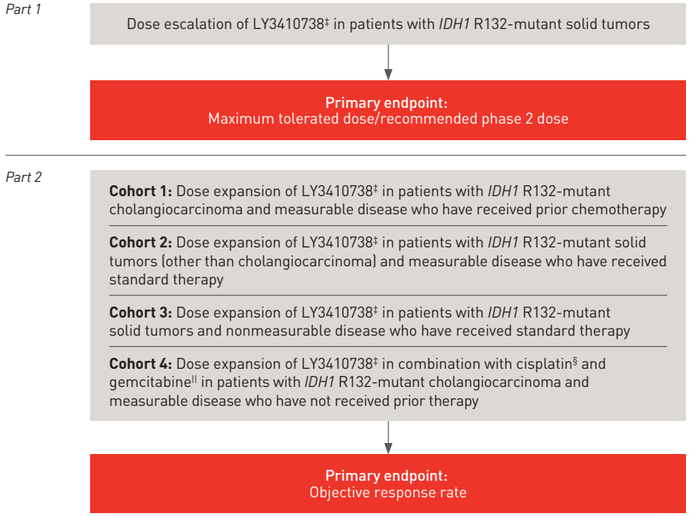
LY3410738 is being investigated in clinical trials in patients with advanced hematologic malignancies or advanced solid tumors.

References: 1. Waitkus MS, et al. *Cancer Cell.* 2018;34(2):186-195. **2.** Gross S, et al. *J Exp Med.* 2010;207(2):339-344. **3.** Borger DR, et al. *Oncologist.* 2012;17(1):72-79. **4.** Amary MF, et al. *J Pathol.* 2011;224(3):334-343. **5.** Yan H, et al. *N Engl J Med.* 2009;360(8):765-773. **6.** Losman JA, et al. *Science.* 2013;339(6127):1621-1625. **7.** Lu C, et al. *Nature.* 2012;483(7390):474-478. **8.** Brooks N, et al. AACR Annual Meeting; March 29-April 3, 2019; Atlanta, GA. Abstract LB274.

The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

NCT04521686

A Phase 1 Study of LY3410738 Administered to Patients With Advanced Solid Tumors With *IDH1* Mutations*†



* This clinical trial is being conducted in the United States.
† Additional criteria not shown here may exist for individual parts of the study.
‡ LY3410738 is administered PO.
§ Cisplatin is administered intravenously (IV).
|| Gemcitabine is administered IV.

The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

Key Inclusion Criteria

- Evidence of *IDH1* R132 mutation in tumor tissue (any solid tumor) or circulating tumor DNA (cholangiocarcinoma, chondrosarcoma, and glioma) as determined by molecular testing routinely performed at a certified laboratory
- Availability of an archived tumor tissue sample
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- ≥18 years of age
- Adequate organ function
- Able to swallow capsules
- Able to comply with outpatient treatment, laboratory monitoring, and required clinic visits for the duration of study participation
- Adequate biliary drainage (per investigator's discretion) with no evidence of ongoing infection for cholangiocarcinoma patients
- Males and females of reproductive potential must be willing to use conventional and effective birth control
- Primary central nervous system (CNS) tumors with no leptomeningeal disease and are on a stable or decreasing steroid dose for 7 days prior to screening

Key Exclusion Criteria

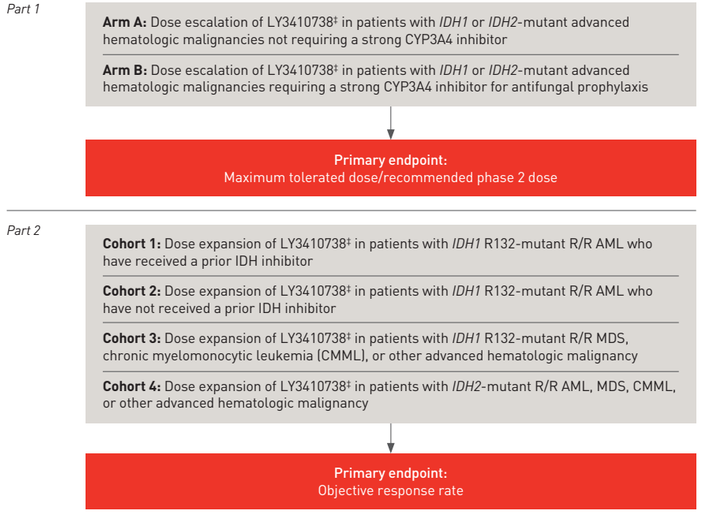
- Investigational agent or anticancer therapy within 2 weeks; or investigational monoclonal antibody within 4 weeks prior to planned start of study treatment
- Major surgery within 4 weeks prior to planned start of study treatment
- Radiotherapy with a limited field of radiation for palliation within 7 days of the first dose of study treatment, except for patients receiving whole-brain radiotherapy, which must be completed at least 4 weeks prior to the first dose of study treatment
- Cholangiocarcinoma that underwent hepatic radiation, chemoembolization and radiofrequency ablation, radioembolization, or other locoregional therapy <4 weeks; history of hepatic encephalopathy of any grade; ascites requiring intervention such as diuretics or paracentesis; ongoing cholangitis; or mixed hepatocellular biliary tract cancer histology
- Active CNS metastases or suspected or confirmed leptomeningeal disease (patients with asymptomatic and treated brain metastases may participate provided that they are stable and are not requiring steroid treatment)
- Evidence of intracranial hemorrhage either by MRI or CT
- Any unresolved toxicities from prior therapy > grade 2 as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 at the time of starting study treatment, except for alopecia
- Clinically significant, uncontrolled cardiac or cardiovascular disease, or prolongation of the QT interval corrected for heart rate (QTcF) >470 msec on at least two out of three consecutive electrocardiograms (ECGs), and mean QTcF >470 msec on all three ECGs, during screening; or history of myocardial infarction within 6 months prior to planned start of study treatment
- Active, uncontrolled systemic bacterial, viral, fungal, or parasitic infection (except for fungal nail infection), or other clinically significant active disease process
- Known HIV infection and/or active hepatitis B or C infection (patients with controlled hepatitis B or successfully treated hepatitis C >4 weeks between achieving sustained viral response and starting study drug are eligible)
- Treatment with certain strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers and/or strong P-gp inhibitor
- Treatment with proton pump inhibitor within 7 days of starting study drug
- Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of the study treatment
- Active second malignancy unless in remission and with life expectancy >2 years
- Pregnancy, lactation, or plan to breastfeed during the study or within 30 days of the last dose of study treatment
- Hypersensitivity to any component of the study drug or its formulation

LOXO ONCOLOGY at Lilly

Please visit **www.clinicaltrials.gov** for more information on this clinical trial [NCT04521686].

NCT04603001

A Phase 1 Study of Oral LY3410738 in Patients With Advanced Hematologic Malignancies With *IDH1* or *IDH2* Mutations*†



* This clinical trial is being conducted in the United States.
† Additional criteria not shown here may exist for individual parts of the study.
‡ LY3410738 is administered PO.

The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

Key Inclusion Criteria

- ≥18 years of age or age of majority if higher per local regulations
- Advanced *IDH*-mutant hematologic malignancy, including acute myeloid leukemia (AML) according to the World Health Organization (WHO) 2016 criteria, myelodysplastic syndrome (MDS) with excess blasts (subtype MDS-EB-1 or MDS-EB-2) or considered high or very high risk by the Revised International Prognostic Scoring System (IPSS R), or other relapsed and/or primary refractory (R/R) hematologic cancers (eg, chronic myelomonocytic leukemia or myeloproliferative neoplasms [myelofibrosis, essential thrombocythemia, or polycythemia vera])
- Blasts at least 5% in bone marrow
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
- Adequate organ function
- Able to swallow capsules
- Able to comply with outpatient treatment, laboratory monitoring, and required clinic visits for the duration of study participation
- Males and females of reproductive potential must be willing to use conventional and effective birth control

Key Exclusion Criteria

- Investigational agent or anticancer therapy within 2 weeks or 5 half-lives, whichever is shorter; or investigational monoclonal antibody within 4 weeks prior to planned start of study treatment with the exception of hydroxyurea, which is allowed throughout the study for the control of peripheral leukemia blasts in patients with white blood cell counts >30,000/µL
- Major surgery within 4 weeks prior to planned start of study treatment
- Active, uncontrolled clinically significant systemic bacterial, viral, fungal, or parasitic infection, or an unexplained fever >101.3°F during screening or on the first day of study treatment
- Another concurrent malignancy requiring active therapy
- Active central nervous system involvement
- Any unresolved toxicities from prior therapy > grade 2 as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 at the time of starting study treatment, except for alopecia
- History of hematopoietic stem cell transplant, or CAR-T therapy within 60 days of the first dose of study treatment, or with any of the following:
  - Ongoing immunosuppressive therapy post-HSCT or CAR-T therapy at the time of screening with the exception of use of low-dose corticosteroids ≤10 mg prednisone or equivalent and topical steroids for ongoing skin graft-versus-host disease (GVHD), or clinically significant GVHD, or need for anticytokine therapy for toxicity from CAR-T therapy; residual symptoms of neurotoxicity > grade 1 from CAR-T therapy
- Clinically significant cardiovascular disease with history of myocardial infarction within 6 months prior to planned start of study treatment; New York Heart Association (NYHA) class III or IV congestive heart failure; unstable angina; LVEF <40% by echocardiogram (ECG) or multigated acquisition scan within 28 days of C1D1; known history of severe and/or uncontrolled ventricular arrhythmia within 6 months prior to planned start of study drug; prolongation of the QT interval corrected for heart rate (QTcF) >470 msec on at least two out of three consecutive ECGs, and mean QTcF >470 msec on all three ECGs, during screening
- Active HIV and/or hepatitis B or C virus (patients with controlled hepatitis B or successfully treated hepatitis C >4 weeks between achieving sustained viral response and starting study drug are eligible)
- Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of the study drug
- Current treatment with certain strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers and/or strong p-gp inhibitor with the exception of patients being treated with allowed antifungal inhibitors of CYP3A4 who are being evaluated for arm B
- Treatment with proton pump inhibitor within 7 days of starting study drug
- Any serious underlying medical or psychiatric condition, dementia, or altered mental status, or any issue that would impair the ability of the patient to understand informed consent or that in the opinion of the investigator would contraindicate the patient's participation in the study or confound the results of the study
- Pregnancy, lactation, or plan to breastfeed during the study or within 30 days of the last dose of study treatment
- Known hypersensitivity to any components of the study drug or its formulation

LOXO ONCOLOGY at Lilly

Please visit **www.clinicaltrials.gov** for more information on this clinical trial [NCT04603001].

LOXO ONCOLOGY at Lilly

Pipeline information is current through April 27, 2021.

VV-OTHR-US-DEL-0492 04/2021 PRINTED IN USA