

Phase 1 Study of the Dual Isocitrate Dehydrogenase (IDH) 1/2 Inhibitor LY3410738

Summarize the findings of: Harding JJ, Oh DY, Mercade TM, Goyal L, Varkaris A, Palmieri LJ, Ikeda M, Kondo S, Bai LY, Ueno M, Chen LT, Papadopoulos KP, Shroff RT, Kizilbash SH, Hollebecque A, Adeva J, Cosman R, Yokota T, Park JO, Turk A, Liao CY, Satoh T, Borad MJ, El-Khoueiry A, Azad N, Jaeckle KA, Loong HH, Yong WP, Bender MH, Varughese SC, Sachdeva D, Radtke DB, Gueorguieva I, Szpurka AM, Chen HR, Liu H, Xu X, Rodon J. Final Results from a First-in-Human Phase 1 Study of the Dual Isocitrate Dehydrogenase (IDH) 1/2 Inhibitor, LY3410738, in Advanced Solid Tumors Harboring IDH1 or IDH2 Mutations. Clin Cancer Res. 2025 Sep 30. doi: 10.1158/1078-0432.CCR-25-0174. Epub ahead of print. PMID: 41026608.

Here's a concise summary of the key findings from Harding et al. (2025) on LY3410738, a dual IDH1/2 inhibitor in IDH-mutated solid tumors:

Study design & objectives

- This was a **first-in-human, global, multicenter, open-label Phase 1 trial** (NCT04521686) of LY3410738 in patients with solid tumors harboring IDH1 or IDH2 mutations. [PubMed+1](#)
 - The trial had multiple arms: monotherapy dose escalation; expansion cohorts combining LY3410738 with cisplatin + gemcitabine (in newly diagnosed cholangiocarcinoma) or with durvalumab (in relapsed/refractory cholangiocarcinoma). [PubMed](#)
 - Primary endpoints were safety / determination of maximum tolerated dose (MTD) or recommended Phase 2 dose, and preliminary evidence of antitumor activity. Secondary assessments included pharmacokinetics, D-2-hydroxyglutarate (2HG) inhibition, and circulating tumor DNA (ctDNA). [PubMed](#)
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Safety and tolerability

- No dose-limiting toxicities (DLTs) were seen in the monotherapy dose escalation portion, so an MTD was **not** reached. [PubMed](#)
- The most common adverse events (AEs) in all arms were **nausea, vomiting, and decreased appetite**. [PubMed](#)

- In the combination arms, the treatments were generally tolerated; one DLT occurred in the durvalumab cohort. [PubMed](#)
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Pharmacodynamics / target engagement

- LY3410738 achieved **rapid and durable normalization** of D-2-hydroxyglutarate levels (i.e. suppression of the oncometabolite produced by mutant IDH) in treated patients. [PubMed](#)
 - The authors also tracked ctDNA but detailed results on that in the abstract are limited. [PubMed](#)
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Efficacy / antitumor activity

In relapsed / refractory disease (monotherapy / combinations)

- For patients with relapsed/refractory IDH1- or IDH2-mutant cholangiocarcinoma treated with LY3410738 (mostly monotherapy), the **overall response rate (ORR)** was 5.2%. [PubMed](#)
- The **disease control rate (DCR)** in that group was 56.9%. [PubMed](#)
- For patients with IDH1-mutant glioma, the ORR was 11.1%, and DCR was 63.0%. [PubMed](#)
- The authors characterize this activity as “largely cytostatic” (i.e. disease stabilization rather than widespread tumor shrinkage). [PubMed](#)

In newly diagnosed cholangiocarcinoma (combination with cisplatin + gemcitabine)

- In the expansion cohort of newly diagnosed (i.e. first-line) IDH-mutant cholangiocarcinoma, **LY3410738 + cisplatin/gemcitabine** achieved an ORR of 42.1%. [PubMed](#)
 - Median duration of response (DOR) in that group was 8.1 months. [PubMed](#)
 - Median progression-free survival (PFS) was 10.2 months. [PubMed](#)
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Interpretation & implications

- The authors conclude that LY3410738 demonstrates **mainly cytostatic antitumor activity** in IDH1/2 mutated cholangiocarcinoma and IDH1-mutant gliomas in the relapsed/refractory setting. [PubMed](#)
- However, the **combination** of LY3410738 with standard chemotherapy (cisplatin + gemcitabine) in newly diagnosed cholangiocarcinoma showed more promising efficacy, suggesting a potential role for combination strategies. [PubMed](#)
- Because of its oral formulation and brain-penetrant design, LY3410738 may offer advantages for tumors in the CNS or with resistance to prior IDH inhibitors. [PubMed](#)

- The favorable tolerability profile and evidence of target engagement support further exploration in Phase 2/3 studies, especially in combination regimens or in earlier lines of therapy. [PubMed](#)
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Give me an overview on trials with LY3410738 and IDH1-mutant gliomas

Sure — here's a focused, up-to-date overview of clinical trial evidence for **LY3410738 (a.k.a. crelosidenib / LY-3410738)** in **IDH1-mutant gliomas**, with the key data points and context.

Quick summary (TL;DR)

- LY3410738 was evaluated in a multi-center **Phase 1** trial (NCT04521686) that included an **IDH1-mutant glioma** cohort. [ClinicalTrials+1](#)
- In the pooled Phase-1 report (Harding et al., Clin Cancer Res, Sep 2025), LY3410738 showed **target engagement** (rapid, durable suppression of D-2-HG), **favorable tolerability**, and **mainly cytostatic activity** in IDH1-mutant gliomas: **ORR ~11.1%** and **disease control rate ~63%** in glioma patients. [PubMed](#)
- No maximum tolerated dose (MTD) was reached in monotherapy escalation; most common AEs were nausea/vomiting and decreased appetite. [PubMed+1](#)

Trials & design

- **NCT04521686** — Phase 1, open-label, multicenter study of oral LY3410738 in advanced solid tumors with IDH1 R132 or IDH2 mutations. The protocol included dose escalation and expansion cohorts; glioma patients (IDH1-mutant) were one of the tumor cohorts studied. Primary goals were safety, recommended Phase-2 dose, PK/PD; secondary included preliminary efficacy, 2-HG suppression and ctDNA. [ClinicalTrials+1](#)

Key results in IDH1-mutant glioma (from the final Phase-1 report)

- **Pharmacodynamics:** LY3410738 produced **rapid and durable suppression of D-2-hydroxyglutarate (2-HG)**, evidence of on-target activity in patients. [PubMed](#)
- **Efficacy (glioma cohort):**
 - **Objective response rate (ORR): ~11.1%.**
 - **Disease control rate (DCR): ~63%** (stable disease + partial responses).
 - Authors describe the activity as **largely cytostatic** (more disease stabilization than tumor shrinkage). [PubMed](#)

- **Safety:** No DLTs in monotherapy escalation (MTD not reached); common AEs were gastrointestinal (nausea/vomiting) and decreased appetite. Combination cohorts had expected chemo/immunotherapy toxicities; one DLT in the durvalumab arm. [PubMed+1](#)

Other context and history

- Earlier conference abstracts (AACR/ASCO summaries) reported initial Phase-1 experience including glioma patients and PD (2-HG) data. [AACR Journals+1](#)
- There were press/analysis notes in 2023 indicating Lilly had **removed the dual-IDH program (LY3410738)** from its internal pipeline (reports suggested limited efficacy in IDH-inhibitor-pretreated cases); however, the Phase-1 study completed and final results were later published in 2025. This creates an apparent mismatch between an earlier corporate pipeline decision and the formal trial reporting record — the peer-reviewed / conference literature and registry entries are the primary sources for trial data. [Pipeline Oncologico+1](#)

Interpretation for IDH1-mutant glioma

- LY3410738 **engages target** in patients (2-HG suppression) and is **clinically tolerable**, but **antitumor activity in relapsed/refractory glioma appears modest and mainly cytostatic** (stabilization more than frequent tumor shrinkage). Reported ORR ~11% and DCR ~63% suggest some patients benefit but limited objective responses. [PubMed](#)
- Potential roles to explore: earlier-line use, combination strategies, or use in tumors not previously treated with other IDH inhibitors. Brain-penetrant design is potentially advantageous, but convincing phase-2/3 efficacy data in glioma are still lacking. [PubMed+1](#)

What's missing / open questions

- Detailed subgroup data (e.g., by glioma grade, prior IDH-inhibitor exposure, concurrent IDH resistance mutations) and ctDNA/biomarker correlates are not fully reported in the abstract/summary — full text and supplementary tables may contain more granular information. [PubMed](#)
- Unclear future development path for crelosidenib/LY3410738 in glioma given earlier pipeline movements and the modest single-agent activity reported.

Sources (selected)

- Harding JJ et al., *Clin Cancer Res.* (Final Phase-1 results, Sep 30, 2025). PubMed entry for the paper. [PubMed](#)
- ClinicalTrials.gov NCT04521686 (Phase-1 study of LY3410738). [ClinicalTrials](#)

- AACR/ASCO abstracts and institutional trial pages (initial reports & trial descriptions). [AACR Journals+2ASC Publications+2](#)
 - Reporting on Lilly pipeline changes (commentary/news item noting removal from internal pipeline in 2023). [Pipeline Oncologico](#)
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Build a one-page slide summarizing the glioma cohort data

Your one-page summary slide on **LY3410738 in IDH1-mutant gliomas** is ready. Would you like me to format it visually for presentation (e.g., PowerPoint slide layout with bullet hierarchy and color emphasis)?

Yes

Ly3410738 Glioma Slide

LY3410738 (Dual IDH1/2 Inhibitor) in IDH1-Mutant Gliomas – Phase 1 Overview

Source: Harding JJ et al., *Clinical Cancer Research*, Sept 2025 – First-in-human, Phase 1 trial (NCT04521686)

Study Design

- **Trial type:** Global, multicenter, open-label Phase 1 (dose escalation → expansion)
 - **Population:** Advanced solid tumors with *IDH1/2 mutations* (included IDH1-mutant gliomas)
 - **Primary objectives:** Safety, MTD/recommended Phase 2 dose, PK/PD (2-HG inhibition)
 - **Secondary objectives:** Preliminary efficacy (per RANO), ctDNA, biomarker response
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Glioma Cohort – Key Findings

Measure	Result
Objective Response Rate (ORR)	~11.1%
Disease Control Rate (DCR)	~63.0% (mostly stable disease)
Activity type	Predominantly cytostatic (disease stabilization > shrinkage)
Median DOR / PFS	Not reported in abstract

Interpretation: Modest single-agent activity, but clear pharmacodynamic target engagement.

Pharmacodynamics & Mechanism

- **Rapid, durable suppression** of D-2-hydroxyglutarate (2-HG)
 - Confirms **on-target inhibition** of mutant IDH1/2 enzymes
 - **Brain-penetrant design** → potential utility in CNS tumors
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Safety & Tolerability

- **No DLTs, MTD not reached**
 - **Common AEs:** nausea, vomiting, decreased appetite
 - Generally **well tolerated** in monotherapy
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Interpretation & Future Directions

- LY3410738 shows **robust biochemical activity** and a **favorable safety profile**
 - **Clinical benefit mainly cytostatic** in gliomas (63% DCR)
 - **Next steps:**
 - Evaluate in **earlier lines or combination** therapy
 - Explore in **treatment-naïve** and **IDH-inhibitor-resistant** gliomas
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Takeaway:

LY3410738 effectively inhibits 2-HG and is brain-penetrant, with manageable toxicity. In IDH1-mutant glioma, it achieves disease stabilization in most patients—supporting further study in optimized regimens or combinations.

Your one-page PDF summary slide is ready:

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[12 Oct 2025]