CT109

A first-in-human phase 1 study of LY4050784, an oral, potent, and selective SMARCA2 inhibitor, in patients with advanced solid tumors with *SMARCA4* alterations (Trial in Progress)

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Background

- *SMARCA4* (*BRG1*) alterations occur in approximately 7% and 10% of all solid tumors and NSCLC, respectively, and are associated with worse overall survival[1,2]
- *SMARCA4* mutations create a dependency on SMARCA2 (BRM), resulting in synthetic lethality when SMARCA2 is selectively inhibited (**Fig 1**)[3]
- LY4050784 is an oral, potent, and selective SMARCA2 inhibitor that has demonstrated robust synthetic lethality with single-agent tumor regressions across multiple murine models of *SMARCA4*-mutated NSCLC (**Fig 2**)[4]
- LY4050784 (FHD-909) is being developed in partnership with Foghorn Therapeutics

Fig 1: LY4050784 Mechanism of Action

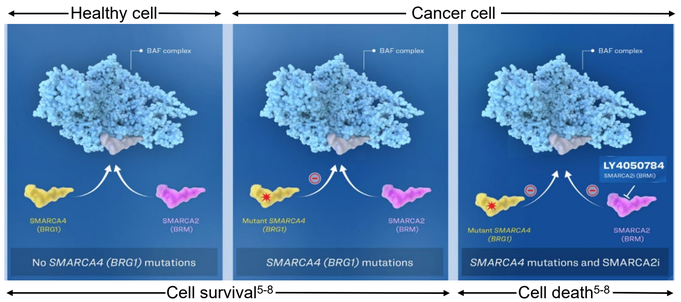
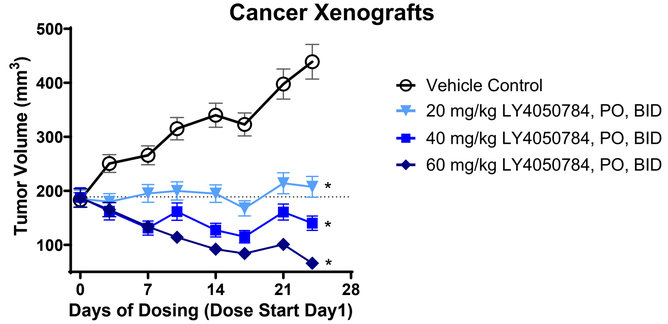


Fig 2: Antitumor Efficacy in SMARCA4/BRG1-Mutant Lung Cancer Xenografts



Data are mean ± SEM. *p ≤ 0.001 compared to vehicle control. NCI-H1793 cells were implanted into mice and treated with LY4050784 at indicated doses. All doses were well-tolerated. Dosing holidays were applied at the high dose, as appropriate

Eligibility Criteria

- Adults (≥18 years) with ECOG PS 0-1
- Have a locally advanced or metastatic cancer and measurable or non-measurable disease (phase 1a dose escalation only) per RECIST v1.1
- Have an eligible SMARCA4 alteration
- Patients must have received all standard therapies for which they were deemed to be an appropriate candidate
- No known loss of function *SMARCA2* alteration or malignancy with known association with *SMARCA2* alterations
- No significant cardiovascular disease, increased risk of prolonged QT, or significant arrythmia
- No known untreated or uncontrolled CNS metastases, or active or recently treated second primary malignancy

Study Design

This is a first-in-human, phase 1a/b open-label, multicenter study of LY4050784, an oral, potent and selective SMARCA2 inhibitor, in patients with advanced solid tumors with *SMARCA4* alterations (NCT06561685)

Phase 1a Dose Escalation

Advanced solid tumors with any *SMARCA4* alteration
- mTPI-2 method with backfilling[a]

Dose Level n
Dose Level 3
Dose Level 2
Dose Level 1

Phase 1b Dose Expansion[b]
Presence of a known or likely loss of function of *SMARCA4*

Part A: 2L + NSCLC[c]
- Optional Randomized Dose Optimization

Randomized → Cohort A1; Cohort A2 (optional); Cohort A3 (optional)

Part B: Other Solid Tumors → Cohort B1

[a]Each dose level will enroll 3-6 DLT-evaluable patients; select dose levels may backfill up to 20 patients; N~80; [b]N~80; [c]Prior platinum doublet, immunotherapy, and antibody-drug conjugate therapy allowed; sponsor may initiate a randomized dose optimization cohort within phase 1b across 2 or more dose levels

- LY4050784 is administered orally BID, in 28-day cycles
- Phase 1b may begin prior to completion of backfill in phase 1a
- In phase 1b, no prior SMARCA2 (BRM) inhibitors/degraders are allowed

Objectives

Phase 1a Dose Escalation

Primary Objective	Secondary Objectives
Assess safety and tolerability of LY4050784 Determine RP2D/MTD of LY4050784	Characterize PK Assess anti-tumor activity of LY4050784 per RECIST v1.1

Phase 1b Dose Expansion and Dose Optimization

Primary Objectives	Secondary Objective
Assess anti-tumor activity of LY4050784 for each cohort Confirm RP2D/optimal dose of LY4050784 (Dose optimization only)	Determine the safety and tolerability of LY4050784

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Participating Countries

- United States
- Japan

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Abbreviations: BAF, BRM or BRG1-associated factors; BID, twice daily; BRG1, Brahma Related Gene 1; BRM, Brahma Homologue; BRMi, BRM Inhibitor; DLT, dose-limiting toxicity; RECIST, Response Evaluation Criteria in Solid Tumors