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LY4050784, a selective inhibitor of SMARCA2, demonstrates synergistic activity in combinations with pembrolizumab or KRAS inhibitors

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[4]Foghorn Therapeutics, Cambridge, MA, USA
[5]Eli Lilly and Company, Louisville, CO, USA

Disclosure Information

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Nathan A. Brooks

I have the following relevant financial relationships to disclose:

I am an employee and share holder of Eli Lilly and Company

I will not discuss off label use and/or investigational use in my presentation

Synthetic Lethality: The rationale for targeting SMARCA2 in *SMARCA4*-mutant cancers

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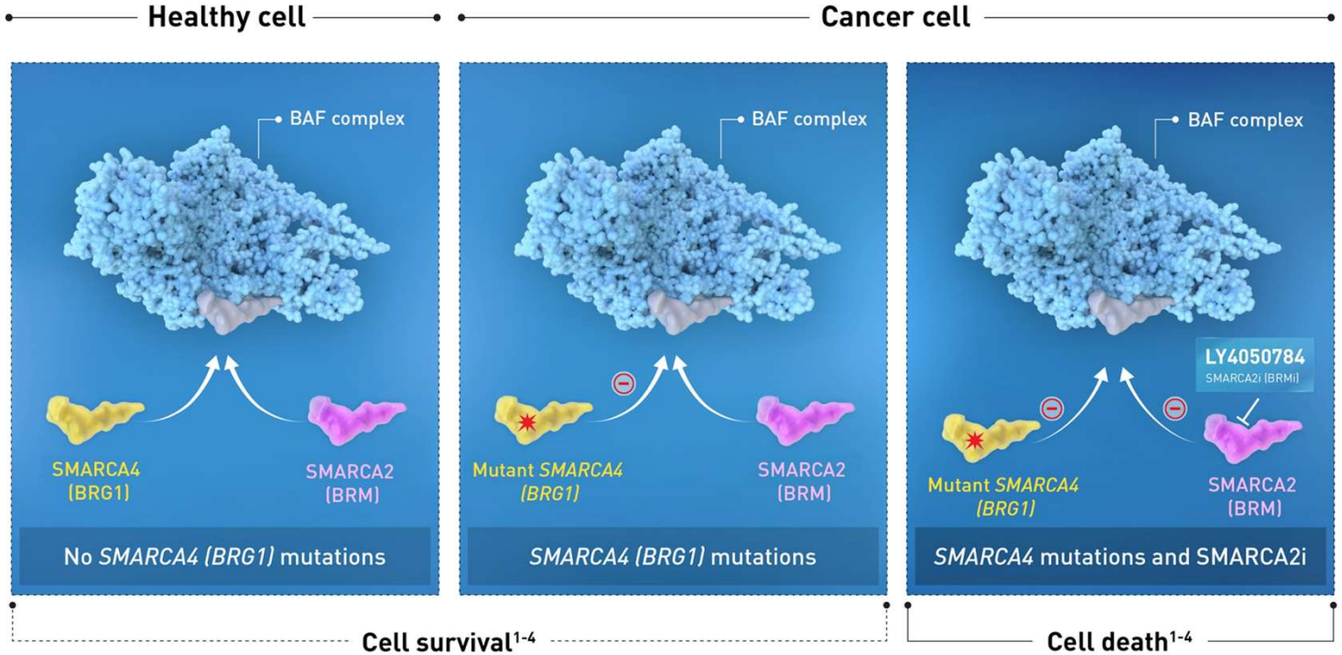

SMARCA2 and SMARCA4 are mutually exclusive ATPases within the BAF complex. When one of the enzymes is lost or damaged, the other compensates for the loss, thus restoring function of the complex.[3-6]

***SMARCA4*-mutant cancer cells rely on SMARCA2 function for the activity of the BAF complex. In this context, inhibition or degradation of SMARCA2 results in synthetic lethality.[3-6]**

BAF=BRM or BRG1-associated factors; BRG1=Brahma Related Gene 1; BRM=Brahma Homologue; BRMi=BRM Inhibitor.

[1]Zhang B, et al. 2021 *Nat Commun.* 12:1275; [2]Jancewicz I, et al., 2019 *Epigenetics Chromatin* 12:68; [3]Papillon JPN, et al., 2018 *J Med Chem.* 61:10155-72; [4]Helming KC, et al., 2014 *Cancer Cell* 26:309-17; [5]Wilson BG, et al., 2014 *Mol Cell Biol.* 34:1136-44; [6]Hoffman GR, et al. 2014 *Proc Natl Acad Sci* USA 111:3128-33

Synthetic Lethality: The rationale for targeting SMARCA2 in *SMARCA4*-mutant cancers

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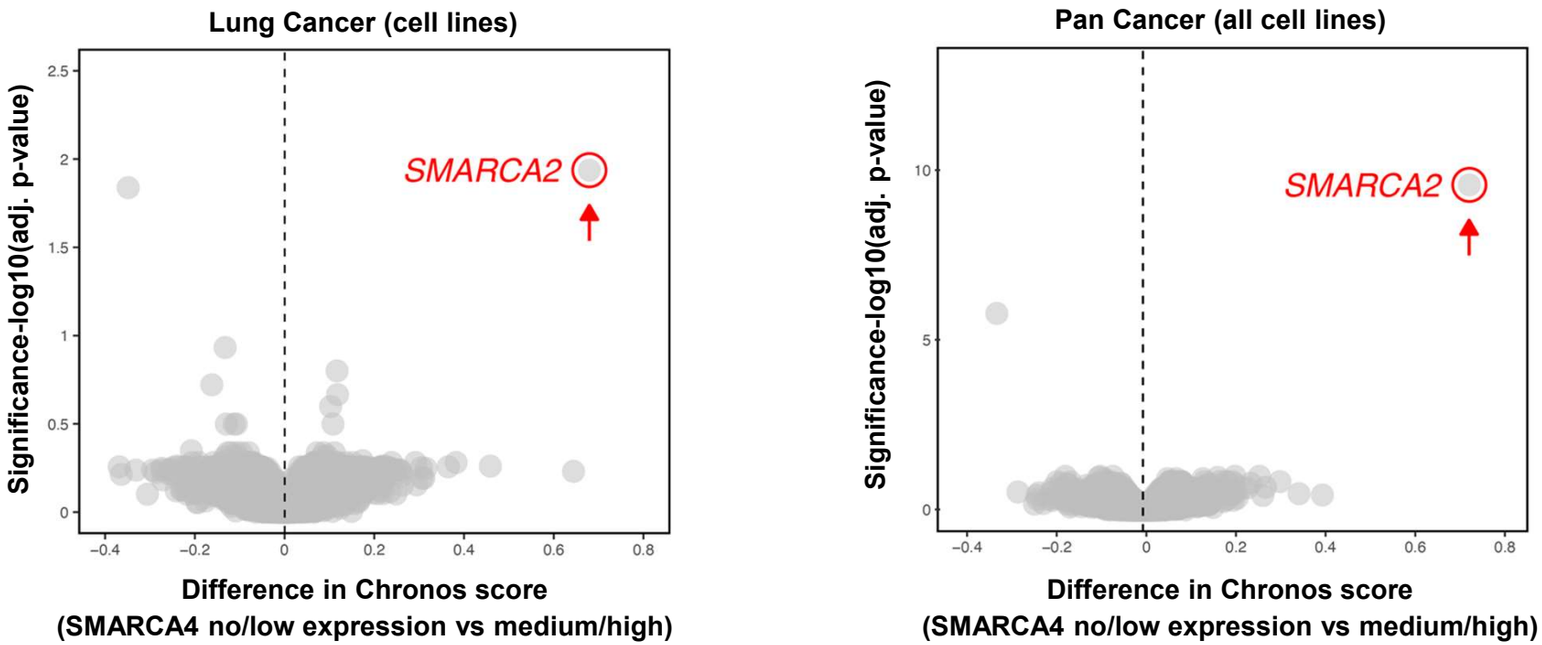
SMARCA2 dependency in SMARCA4 low / mutant cell lines measured by Chronos Score[1]



SMARCA2/SMARCA4 is one of the strongest synthetic lethal dependencies observed in the Broad dependency map data

[1]DepMap Data (October 2023)

LY4050784 shows single agent activity and selectively inhibits growth of *SMARCA4*-mutant tumors

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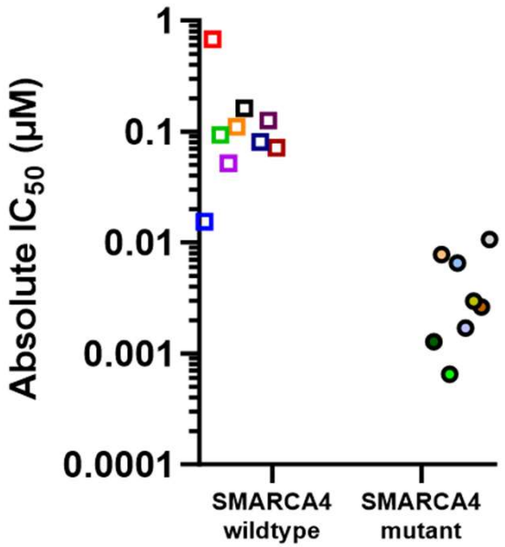
LY4050784 exhibits potent and selective anti-proliferative activity against *SMARCA4*-mutant cells *in vitro*[1]

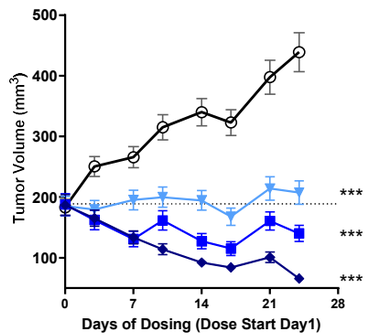


SMARCA2 (WT) SMARCA4 (WT)	SMARCA2 (WT) SMARCA4 (MUT)
NCI-H2122	NCI-H1944
CALU6	NCI-H1299
NCI-H2172	A549
NCI-H441	RERFLCAI
NCI-H2170	NCI-H1693
NCI-H460	NCI-H1568
NCI-H1703	NCI-H2023
NCI-H358	NCI-H838
NCI-H2009	

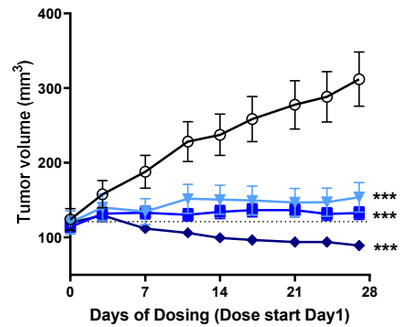
The median IC_{50} of the SMARCA4 WT cell lines is 33-fold higher than median IC_{50} of the SMARCA4 mutant cell lines. 9 WT and 8 MUT cell lines were treated with LY4050784 in a proliferation assay for 10 days. Cell viability was measured using Cell Titer Glo.

- **LY4050784 is an oral, potent, and selective SMARCA2 inhibitor with >30-fold potency against SMARCA2 compared to SMARCA4. LY4050784 provides continuous target coverage at well tolerated doses**
- **LY4050784 demonstrates selective inhibition and killing of *SMARCA4*-mutant tumors and tumor cells**

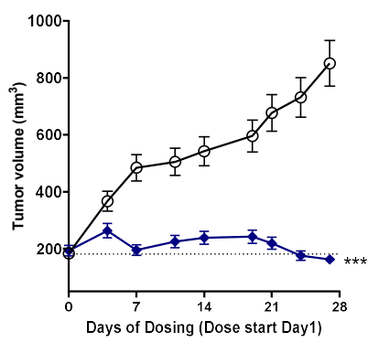
NCI-H1793, Lung model (NSCLC / *SMARCA4*-mutant)



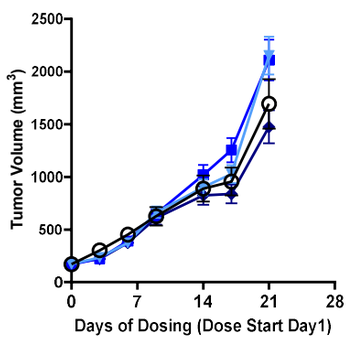
NCI-H2126, Lung model (NSCLC / *SMARCA4*-mutant)



A549, Lung model (NSCLC / *SMARCA4*-mutant)



NCI-H460, Lung model (NSCLC / *SMARCA4*-wildtype)



Studies were conducted in Athymic Nude or NOD SCID gamma (NSG) mice according to all IACUC guidelines. Dosing holidays were applied to the 60mg/kg LY4050784 dose groups as appropriate.

LY4050784 (FHD-909) is being developed in partnership with Foghorn Therapeutics. [1]Lee JY et al, Poster presented at AACR 2024

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Combining LY4050784 with standard of care chemotherapies for lung cancer

Combining LY4050784 with lung cancer chemotherapies – cisplatin and pemetrexed

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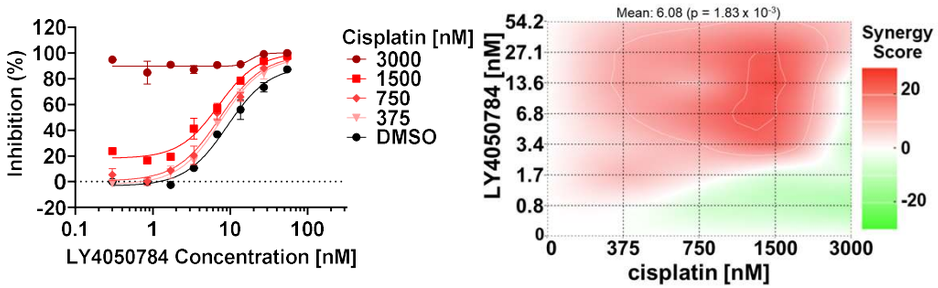
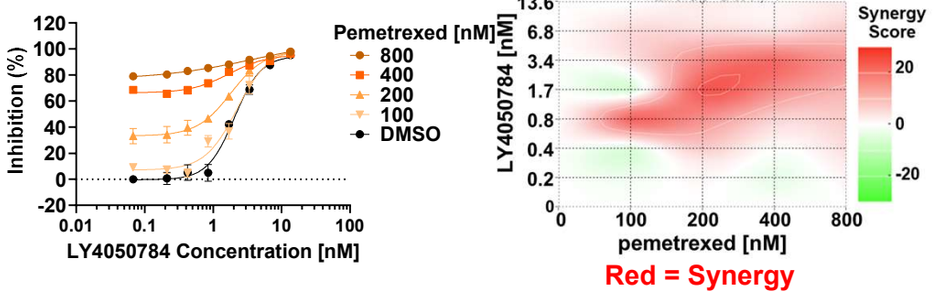
A549, Lung model (NSCLC)

SMARCA4 Q729fs/H736Y, KRAS G12S, STK11 Q37^, KEAP1 G333C, ATR splice

LY4050784 + cisplatin



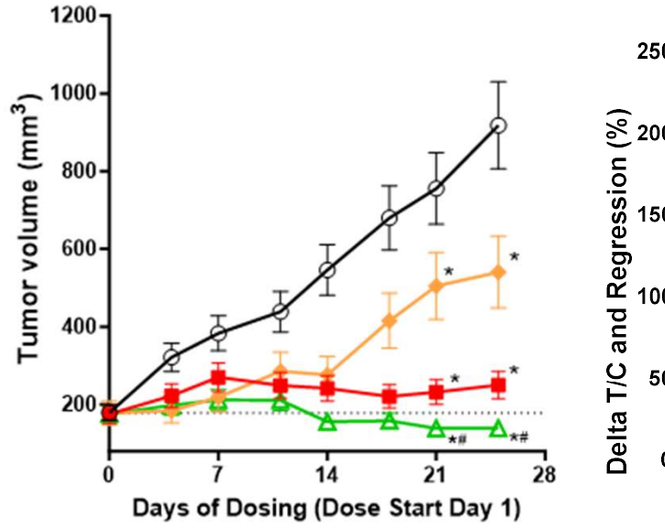
LY4050784 + pemetrexed

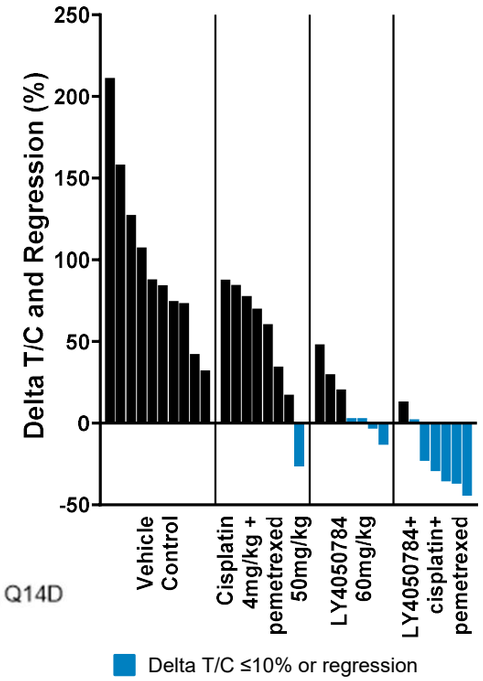


Red = Synergy

Additivity and synergy were observed *in vitro* when LY4050784 was combined with cisplatin or pemetrexed

A549 xenograft model, Nude mice LY4050784+cisplatin+pemetrexed





***In vivo,* combining LY4050784 with cisplatin and pemetrexed increased antitumor effect, resulting in tumor regression**

All combination analyses were performed using Synergy Finder 3.0, HSA. Scores ≤ -10 = antagonistic, -10 to 10 = additive, ≥ 10 = synergistic; mutations: ^early stop; -/- homozygous deletion; fs frameshift. LY4050784 unbound concentrations are reported.

* p≤0.05 for pairwise comparisons for combination group vs vehicle and single agent groups and all treatment groups vs vehicle control, # additive by Bliss Independence analysis. Dosing holidays were applied to the 60mg/kg LY4050784 dose groups as appropriate.

Combining LY4050784 with lung cancer chemotherapies – cisplatin and paclitaxel

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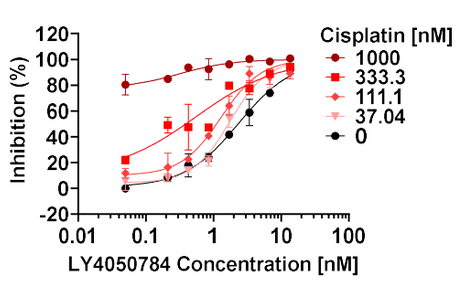
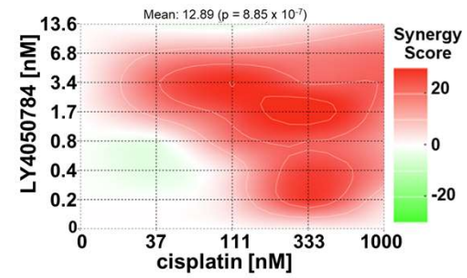
RERF-LC-AI, Lung model (NSCLC)

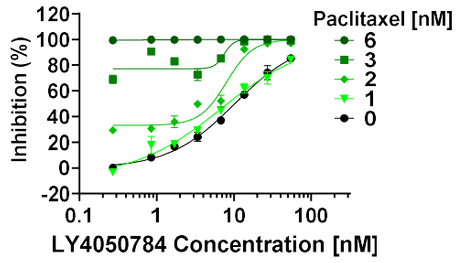
SMARCA4 E1496^, NF1 E1699^, NOTCH4 G796fs

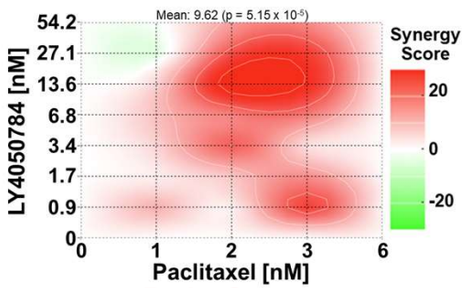
LY4050784 + cisplatin





LY4050784 +paclitaxel

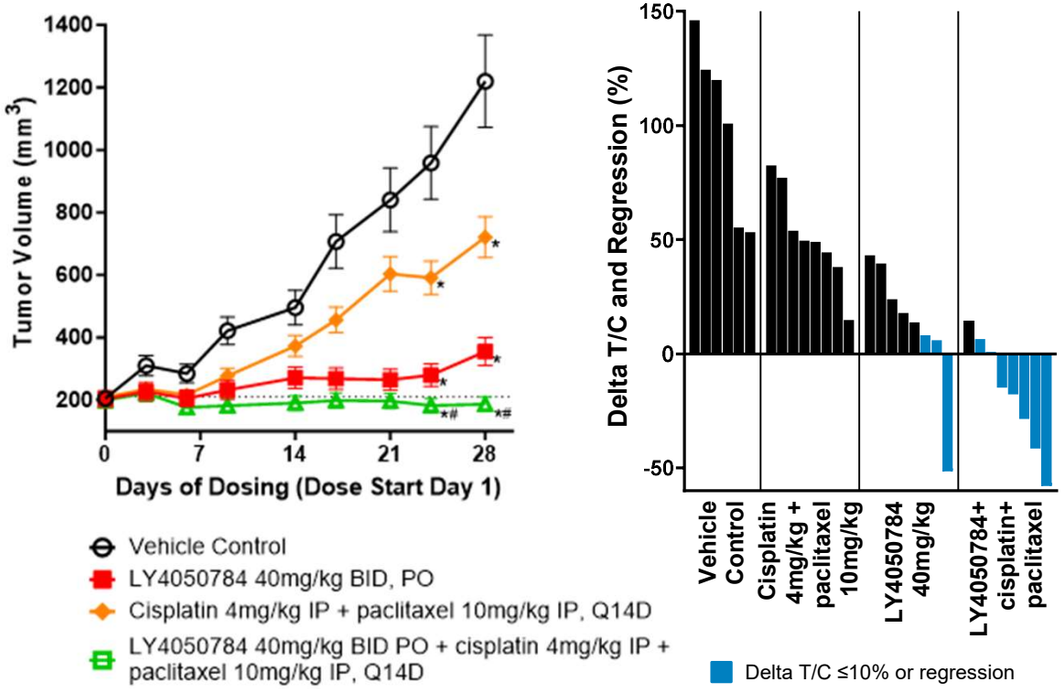




Red = Synergy

Additivity and synergy were observed *in vitro* when LY4050784 was combined with cisplatin or paclitaxel.

RERF-LC-AI xenograft model, Nude mice
LY4050784+cisplatin+paclitaxel



***In vivo,* combining LY4050784 with cisplatin and paclitaxel increased antitumor effect, resulting in tumor regression**

All combination analyses were performed using Synergy Finder 3.0, HSA. Scores ≤ -10 = antagonistic, -10 to 10 = additive, ≥ 10 = synergistic; mutations: ^early stop; -/- homozygous deletion; fs frameshift. LY4050784 unbound concentrations are reported.

* p≤0.05 for pairwise comparisons for combination group vs vehicle and single agent groups and all treatment groups vs vehicle control, # additive by Bliss Independence analysis.

Combining LY4050784 with pembrolizumab

LY4050784 sensitized NSCLC tumor cells to pembrolizumab treatment

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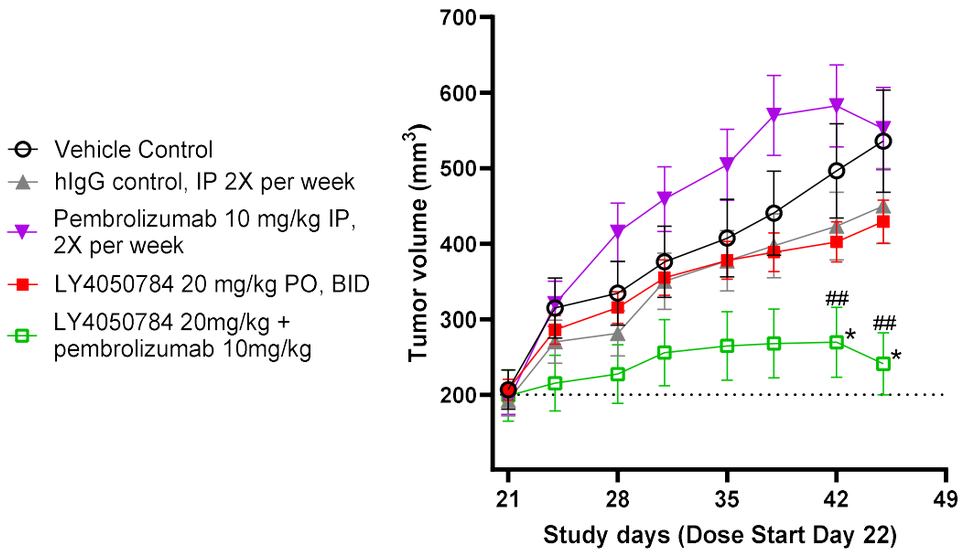
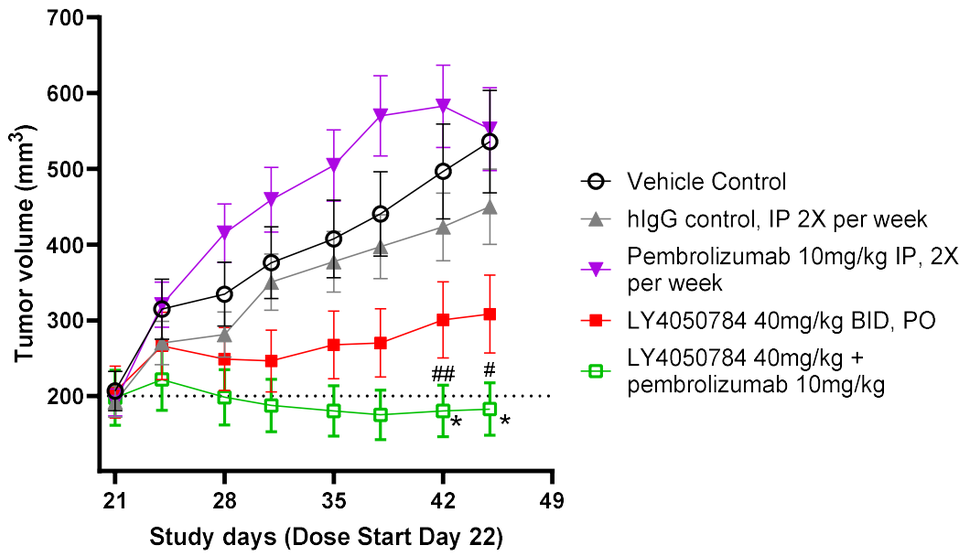
A549 xenograft (CD34+ HSC humanized model)

SMARCA4 Q729fs/H736Y, KRAS G12S, STK11 Q37^, KEAP1 G333C, ATR splice

LY4050784 20 mg/kg + pembrolizumab



LY4050784 40 mg/kg + pembrolizumab



LY4050784 sensitized the tumor cells to pembrolizumab treatment resulting in enhanced combination activity, while pembrolizumab alone had no effect on tumor growth compared to vehicle control

^Early stop; fs frameshift; NSCLC, non small cell lung cancer; *p≤0.05 for pairwise comparisons for combination group vs vehicle and single agents; # additive, ## synergistic by Bliss Independence analysis.

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Combining LY4050784 with selective KRAS inhibitors

KRAS mutations are the most commonly co-occurring driver mutations with SMARCA4 alteration

Synergistic activity observed for LY4050784 in combination with KRAS G12C and pan-KRAS inhibitors

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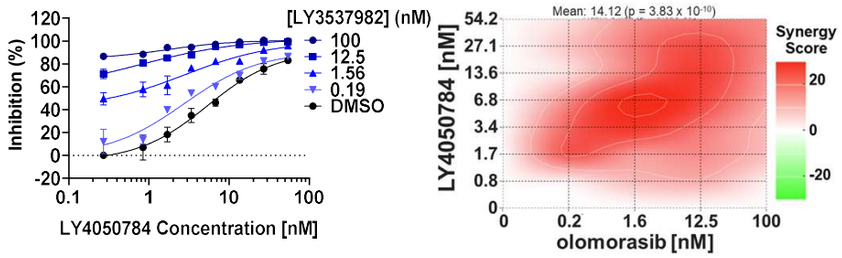
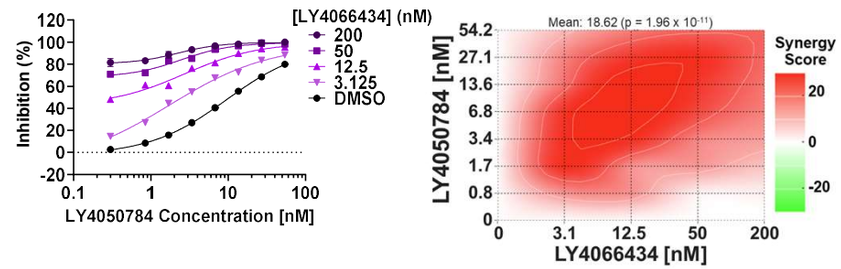
NCI-H2030, Lung model, NSCLC

SMARCA4-/- KRAS(G12C)

LY4050784 + olomorasib (KRAS G12C inhibitor)

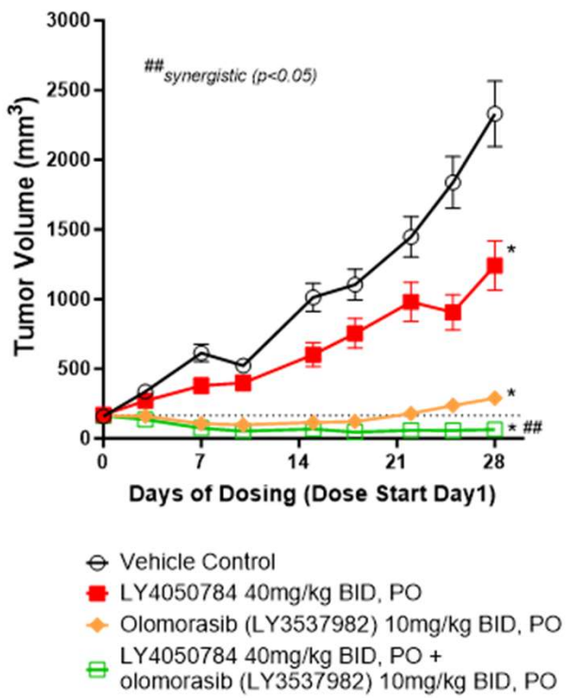


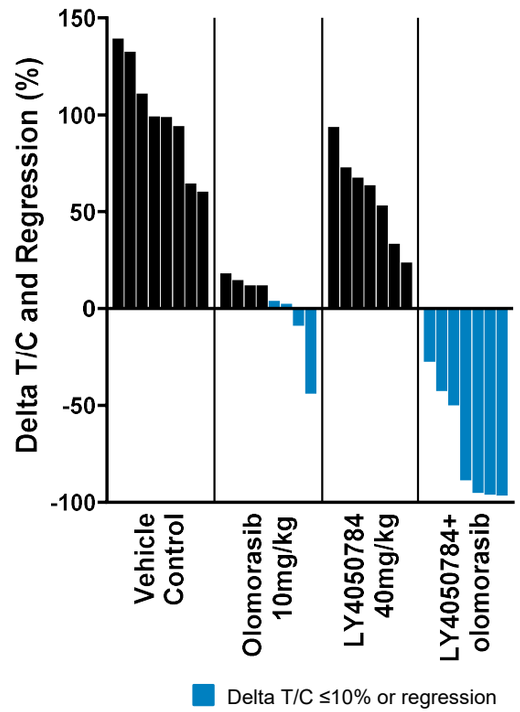
LY4050784 + pan-KRAS inhibitor



Red = Synergy

NCI-H2030 xenograft, NSG mice
LY4050784 + olomorasib





Combining LY4050784 with KRAS G12C selective inhibitor (olomorasib), or isoform selective pan-KRAS inhibitor (LY4066434) resulted in synergistic activity *in vitro*

Combination of LY4050784 with olomorasib demonstrated synergistic antitumor activity and sustained tumor regression *in vivo*

All combination analyses were performed using Synergy Finder 3.0, HSA. Synergy Scores ≤ -10 = antagonistic, -10 to 10 = additive, ≥ 10 = synergistic; -/- homozygous deletion; NSCLC non small cell lung cancer. LY4050784 is reported in unbound concentrations in the assays.

* p≤0.05 for pairwise comparisons for combination group vs vehicle and single agent groups and all treatment groups vs vehicle control, ## synergistic by Bliss Independence analysis. Delta T/C, Change in Treated vs Control

Combinations of LY4050784 with KRAS G12D inhibitor resulted in synergistic activity *in vitro*

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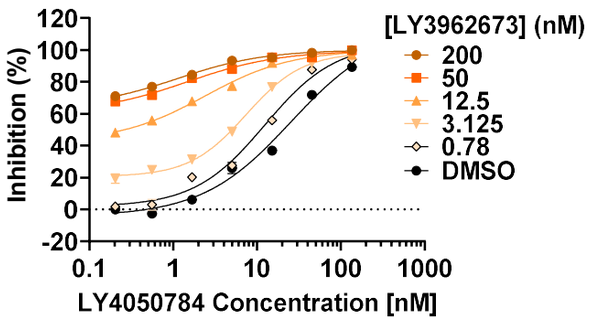
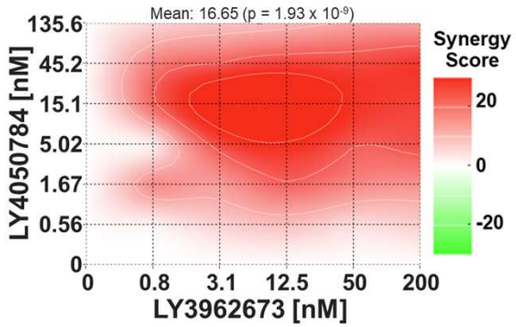
LY4050784 + KRAS G12D inhibitor (LY3962673)

PATU-8988T, Pancreas, PDAC

*SMARCA4 - / fusion, KRAS(G12D)**

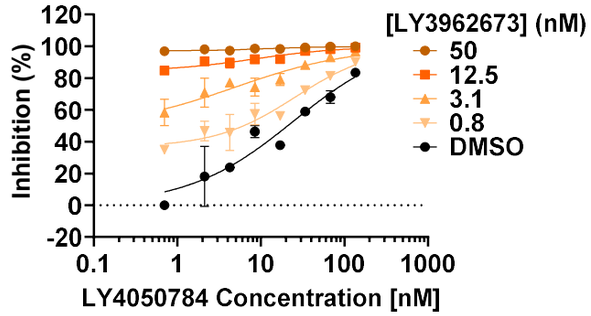


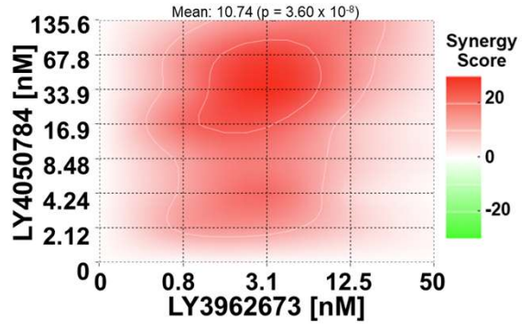


Red = Synergy

SNU-407, Colon, CRC

SMARCA4 P109fs194, R466C, Y507H, M1109V, KRAS(G12D)





Red = Synergy

Synergy was observed for combinations of LY4050784 with KRAS G12D selective inhibitor *in vitro*

All combination analyses were performed using Synergy Finder 3.0, HSA. Synergy Scores ≤ -10 = antagonistic, -10 to 10 = additive, ≥ 10 = synergistic; -/- homozygous deletion; PDAC pancreatic cancer; CRC colorectal cancer, *CRISPR KI. LY4050784 is reported in unbound concentrations in the assays.

Synergistic activity observed for LY4050784 in combination with pan-KRAS inhibitor

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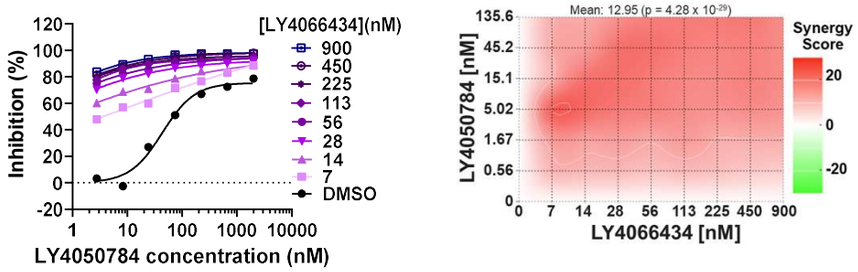
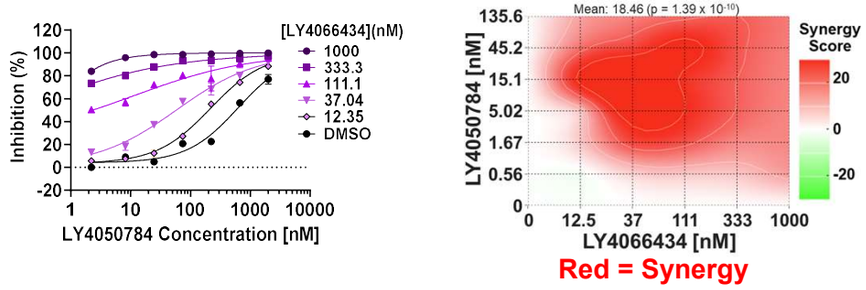
A549, Lung, NSCLC

SMARCA4 Q729fs/H736Y, KRAS(G12S)



PATU-8988T, Pancreas, PDAC

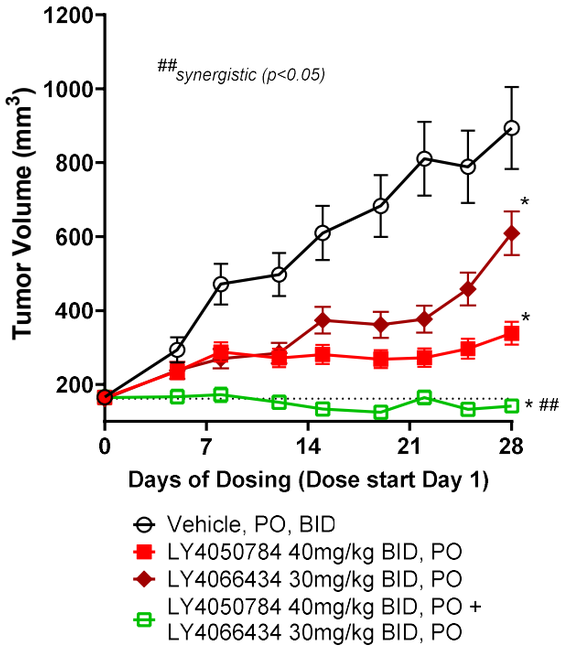
SMARCA4 - / fusion, KRAS(G12V)

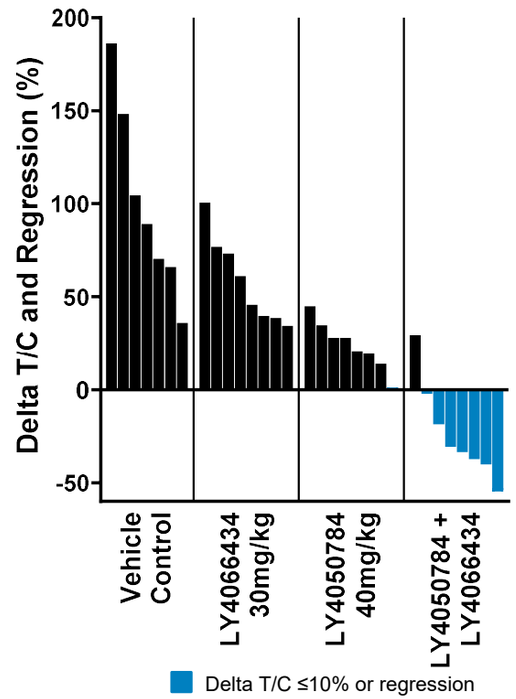


Red = Synergy

Synergy was observed for *in vitro* combinations of LY4050784 with pan-KRAS inhibitor (LY4066434)

A549 xenograft study, Nude mice





Combination of LY4050784 with pan-KRAS inhibitor (LY4066434) resulted in synergistic antitumor activity and sustained tumor regression, *in vivo*

All combination analyses were performed using Synergy Finder 3.0, HSA. Synergy Scores ≤ -10 = antagonistic, -10 to 10 = additive, ≥ 10 = synergistic; fs frameshift; -/ one copy deletion; NSCLC non small cell lung cancer; PDAC pancreatic cancer. LY4050784 is reported in unbound concentrations in the assays.

* p≤0.05 for pairwise comparisons for combination group vs vehicle and single agent groups and all treatment groups vs vehicle control, ## synergistic by Bliss Independence analysis.

Summary

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- **LY4050784**
  - is a SMARCA2 selective small molecule inhibitor developed for the treatment of *SMARCA4*-mutant tumors
  - demonstrates single-agent efficacy in human NSCLC xenograft models
  - shows selective antitumor activity against *SMARCA4*-mutant tumors compared to *SMARCA4*-wildtype human NSCLC tumor models both *in vitro* and *in vivo*

- **LY4050784 combination therapies**
  - LY4050784 in combination with standard of care chemotherapy agents for lung cancer showed additivity / synergy in SMARCA4-mutant human NSCLC cells both *in vitro* and *in vivo*
  - LY4050784 sensitized the human NSCLC xenograft tumors to standard of care, pembrolizumab resulting in synergistic combination activity, while pembrolizumab alone had no effect on tumor growth compared to vehicle control
  - LY4050784 when combined with KRAS inhibitors demonstrated synergy in *SMARCA4*, *KRAS* co-mutated tumor cells both *in vitro and in vivo* xenograft models

- **A phase 1 study of LY4050784 is ongoing (NCT06561685)**
  - Study details are presented in AACR 2025
  - Date / Time - 4/28/25 / 2-5 PM
  - Poster Section 51, Poster Board 4

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