LY4050784

SMARCA2 (BRM) INHIBITOR

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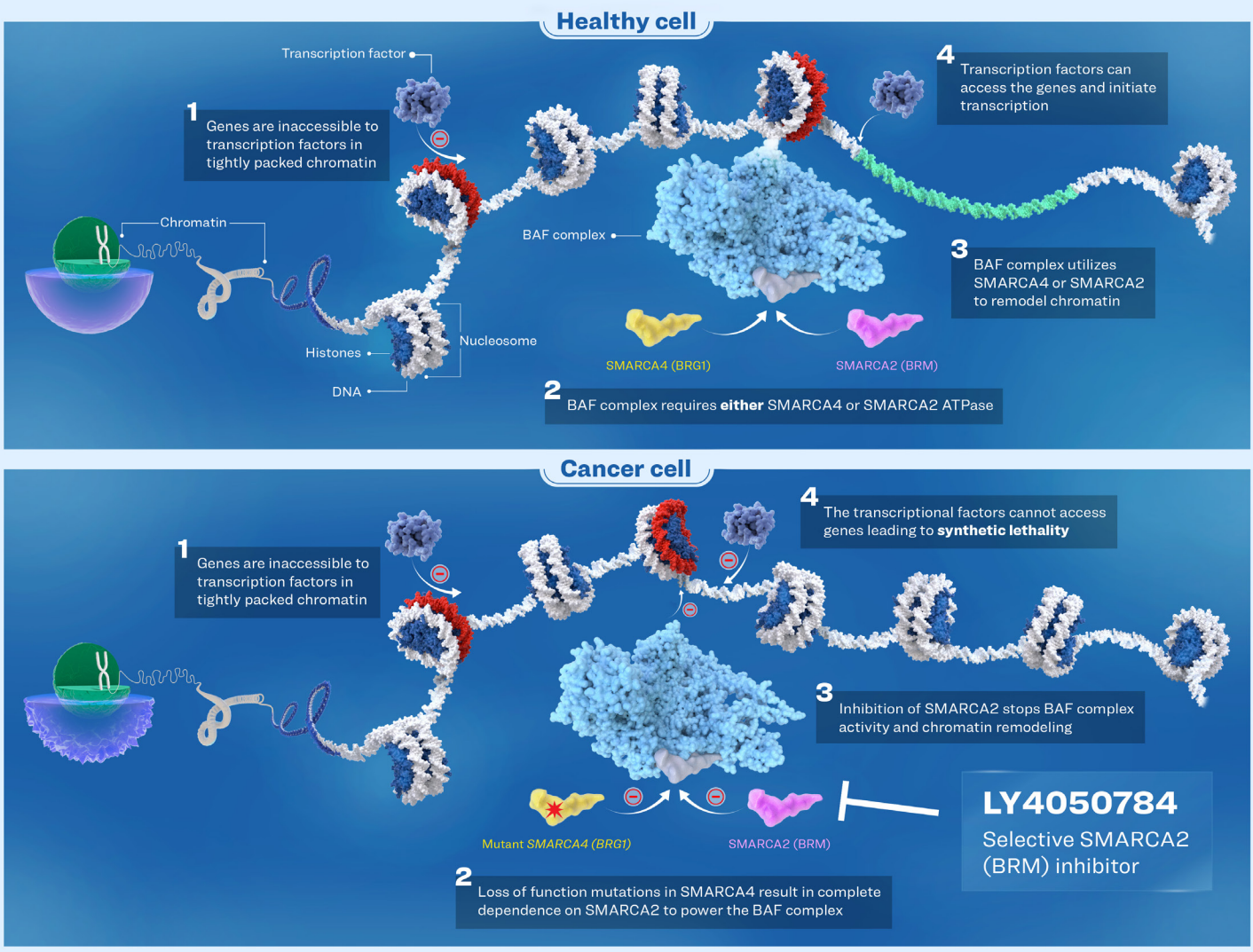
LY4050784 SMARCA2 (BRM) INHIBITOR
MECHANISM OF ACTION[1-6]



Zhang B, et al[1]; Jancewicz I, et al[2]; Papillon JPN, et al[3]; Helming KC, et al[4]; Wilson BG, et al[5]; Hoffman GR, et al[6]

Abbreviations: ATPase=Adenosine Triphosphatase; BAF=BRM/BRG Associated Factor; *BRG1*=Brahma-Related Gene-1; *BRM*=Brahma; DNA=Deoxyribonucleic Acid; SMARCA2=SWI/SNF-Related, Matrix-Associated, Actin-Dependent Regulator of Chromatin, Subfamily A, Member 2; SMARCA4=SWI/SNF-Related, Matrix-Associated, Actin-Dependent Regulator of Chromatin, Subfamily A, Member 4; SWI/SNF=SWItch/Sucrose Non-Fermentable.

References: 1. Zhang B, et al. *Nat Commun.* 2021;12(1):1275. 2. Jancewicz I, et al. *Epigenetics Chromatin.* 2019;12(1):68. 3. Papillon JPN, et al. *J Med Chem.* 2018;61(22):10155-10172. 4. Helming KC, et al. *Cancer Cell.* 2014;26(3):309-317. 5. Wilson BG, et al. *Mol Cell Biol.* 2014;34(6):1136-1144. 6. Hoffman GR, et al. *Proc Natl Acad Sci U S A.* 2014;111(8):3128-3133.

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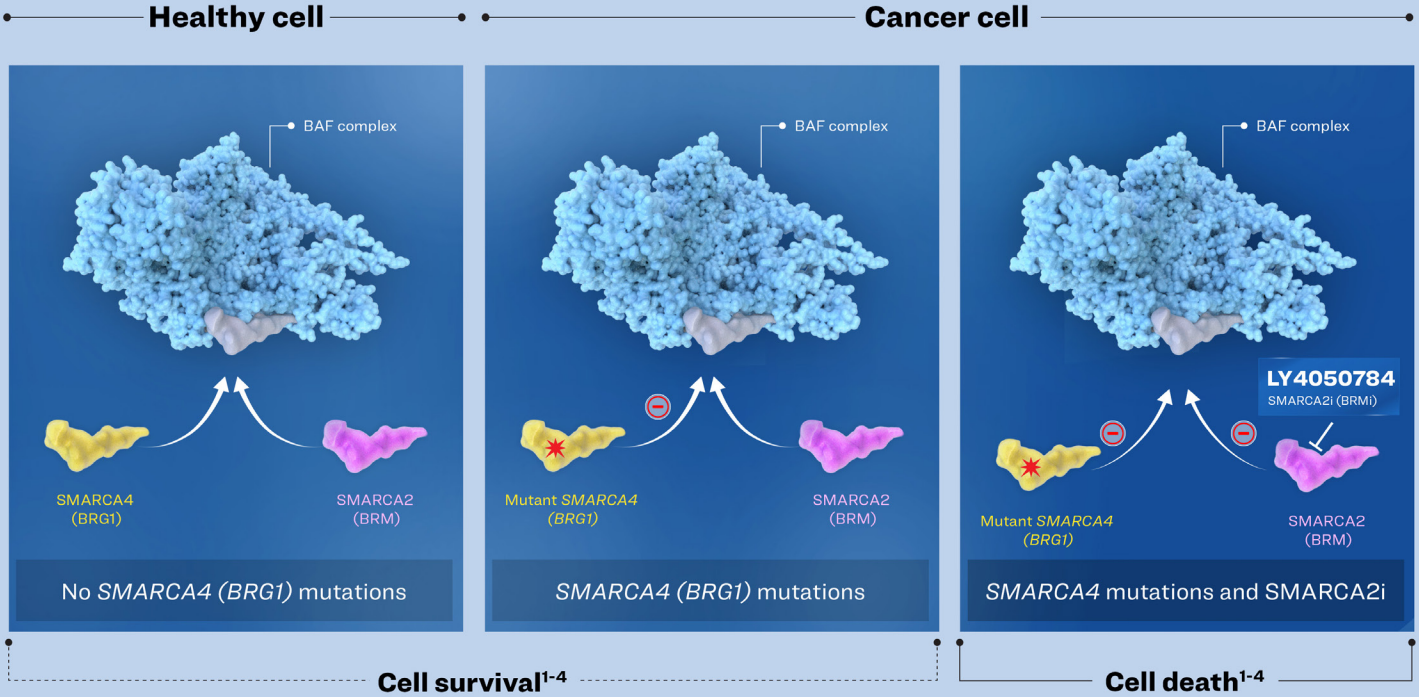
LY4050784 SMARCA2 (BRM) INHIBITOR
MECHANISM OF ACTION[1-6] (Cont.)

Synthetic Lethality

The Rationale for SMARCA2 (BRM) Inhibition in *SMARCA4 (BRG1)* Mutant Cancers



- *SMARCA4* mutant cancer cells are dependent exclusively on SMARCA2 ATPase for survival[3-6]
- Selectively targeting SMARCA2 ATPase is a potential therapeutic option for *SMARCA4*-mutated cancers[3-6]

Zhang B, et al[1]; Jancewicz I, et al[2]; Papillon JPN, et al[3]; Helming KC, et al[4]; Wilson BG, et al[5]; Hoffman GR, et al[6]

Abbreviations: BAF=BRM/BRG Associated Factor; *BRG1*=Brahma-Related Gene-1; *BRM*=Brahma; BRMi=BRM Inhibitor; SMARCA2=SWI/SNF-Related, Matrix-Associated, Actin-Dependent Regulator of Chromatin, Subfamily A, Member 2; SMARCA4=SWI/SNF-Related, Matrix-Associated, Actin-Dependent Regulator of Chromatin, Subfamily A, Member 4; SMARCA2i=SMARCA2 Inhibitor; SWI/SNF=SWItch/Sucrose Non-Fermentable.

References: 1. Zhang B, et al. *Nat Commun.* 2021;12(1):1275. 2. Jancewicz I, et al. *Epigenetics Chromatin.* 2019;12(1):68. 3. Papillon JPN, et al. *J Med Chem.* 2018;61(22):10155-10172. 4. Helming KC, et al. *Cancer Cell.* 2014;26(3):309-317. 5. Wilson BG, et al. *Mol Cell Biol.* 2014;34(6):1136-1144. 6. Hoffman GR, et al. *Proc Natl Acad Sci U S A.* 2014;111(8):3128-3133.

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TARGET

BAF (mSWI/SNF) is a chromatin remodeling complex comprised of multi-protein subunits. BAF requires either SMARCA2 (BRM) or SMARCA4 (BRG1), mutually exclusive ATPase subunits, for chromatin remodeling to occur. Inhibiting SMARCA2 in SMARCA4-deficient cancer is expected to cause synthetic lethality.[1] *SMARCA4* mutations are observed in multiple tumor types, including up to 11% in NSCLCs.[2]

MOLECULE

LY4050784 is a first-in-class potent selective oral SMARCA2 (BRM) inhibitor with greater than 30-fold selectivity for SMARCA2 (BRM) over SMARCA4 (BRG1).[3] Preclinical models have demonstrated tumor regression or tumor growth inhibition in *SMARCA4*-mutant cell lines containing *KRAS, TP53, STK11, and KEAP1.*[3] The competitive pharmacokinetic properties and preclinical data support further advancements into clinical testing.

CLINICAL DEVELOPMENT

LY4050784 is being studied in clinical trials in patients with NSCLC and other solid tumors.

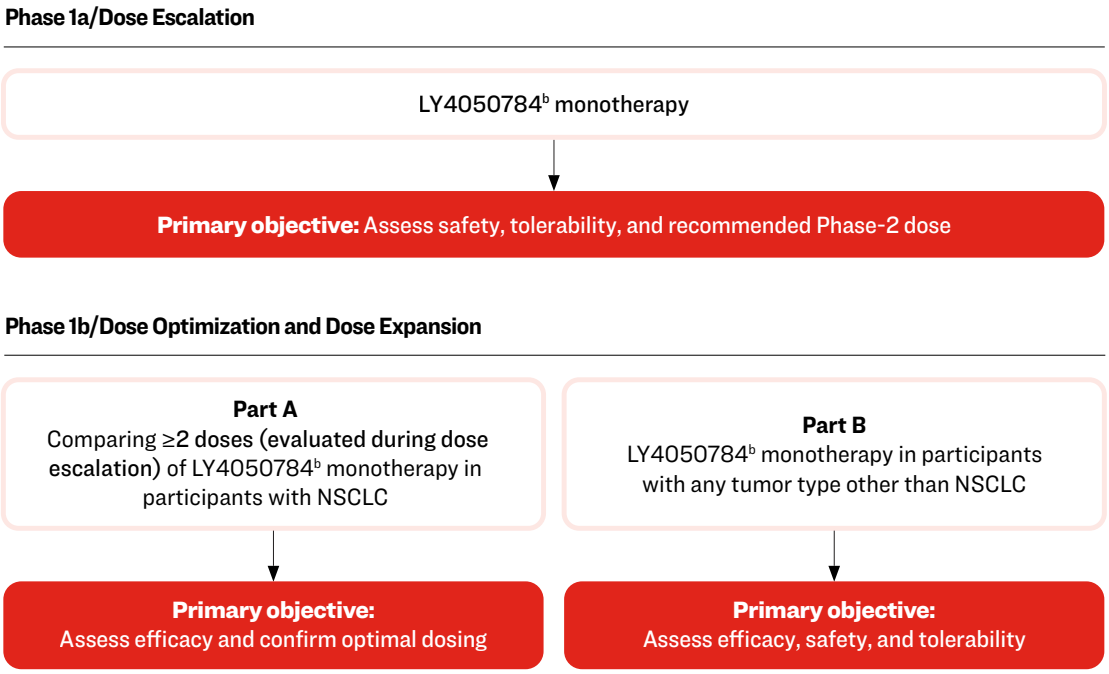
Abbreviations: ATPase=adenosine triphosphatase; BAF=BRM/BRG-Associated Factor; *BRG1*=Brahma-related gene 1; *BRM*=Brahma; KEAP1=Kelch-like ECH-associated protein 1; KRAS=Kirsten Rat Sarcoma Viral Oncogene Homolog; Mammalian SWI/SNF; NSCLC=Non-Small Cell Lung Cancer; SMARCA2=SWI/SNF-Related, Matrix-Associated, Actin-Dependent Regulator of Chromatin, Subfamily A, Member 2; SMARCA4=SWI/SNF-Related, Matrix-Associated, Actin-Dependent Regulator of Chromatin, Subfamily A, Member 4; STK11=Serine/threonine kinase 11; SWI/SNF=SWItch/Sucrose Non-Fermentable; TP53=Tumor Protein p53.

References: 1. Jancewicz I, et al. *Epigenetics Chromatin.* 2019;12(1):68. 2. Dagogo-Jack I, et al. *J Thorac Oncol.* 2020;15(5):766-776. 3. Lee JY, et al. Poster presented at: *AACR 2024*. Poster 3230.

LY4050784 SMARCA2 (BRM) INHIBITOR

NCT06561685

An Open-Label, Multicenter Study of LY4050784, a Selective SMARCA2 (BRM) Inhibitor, in Advanced Solid Tumor Malignancies With *SMARCA4 (BRG1)* Alterations[a]



[a]This clinical trial is being conducted in the United States and Japan. [b]Administered orally.

Abbreviations: *BRG1*=Brahma-Related Gene 1; BRM=Brahma; NSCLC=Non-Small Cell Lung Cancer; SMARCA2=SWI/SNF-Related, Matrix-Associated, Actin-Dependent Regulator of Chromatin, Subfamily A, Member 2; SMARCA4=SWI/SNF-Related, Matrix-Associated, Actin-Dependent Regulator of Chromatin, Subfamily A, Member 4; SWI/SNF=SWItch/Sucrose Non-Fermentable.

Please visit clinicaltrials.gov for more information on this clinical trial [NCT06561685].

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LY4050784 SMARCA2 (BRM) INHIBITOR

NCT06561685

An Open-Label, Multicenter Study of LY4050784, a Selective SMARCA2 (BRM) Inhibitor, in Advanced Solid Tumor Malignancies With *SMARCA4 (BRG1)* Alterations (Cont.)

KEY INCLUSION CRITERIA

- Have one of the following locally advanced or metastatic solid tumor malignancy with *SMARCA4 (BRG1)* alteration:
  - Phase 1a dose escalation: Presence of any alteration in *SMARCA4 (BRG1)*
  - Phase 1b expansion: Part A: NSCLC that is locally advanced and not suitable for definitive locoregional therapy, or metastatic with presence of a known or likely loss of function alteration in *SMARCA4 (BRG1)* or loss of protein expression
  - Phase 1b expansion: Part B: Any tumor type (other than NSCLC) that has the presence of a known or likely loss of function alteration in *SMARCA4 (BRG1)* or loss of protein expression
- Prior systemic therapy criteria:
  - Phase 1a dose escalation and Phase 1b (Part B): Participants who received all standard therapies for which the individual was deemed to be an appropriate candidate by the treating investigator; or the individual is refusing the remaining most appropriate standard of care treatment; or there is no standard therapy available for the disease
  - Phase 1b expansion (Part A): Participants must have received at least one line of therapy for advanced or metastatic disease
- Measurability of disease:
  - Phase 1a dose escalation (excluding backfill): Measurable or non-measurable disease as defined by RECIST v1.1
  - Phase 1a backfill and Phase 1b expansion: Measurable disease required as defined by RECIST v1.1
- Have an ECOG performance status score of 0 or 1

KEY EXCLUSION CRITERIA

- Participants with known loss of function alteration of *SMARCA2 (BRM)* or malignancy with known association with *SMARCA2 (BRM)* alterations
- Prior exposure to SMARCA2 (BRM) inhibitor(s) and/or degrader(s) (prior exposure may be permitted for dose escalation)
- Participants with known or suspected history of untreated or uncontrolled CNS involvement
- Participants with history of increased risk of prolonged QT or significant arrythmia
- Significant cardiovascular disease
- Participants with active or recently treated (within 2 years) second primary malignancy and/or treated for an additional malignancy within 2 years prior to enrolment
- Participants who are pregnant, breastfeeding or plan to breastfeed, or expecting to conceive or father children during the study or within 6 months after the last dose of study intervention

Abbreviations: *BRG1*=Brahma-related gene 1; *BRM*=Brahma; CNS=Central Nervous System; ECOG=Eastern Cooperative Oncology Group; NSCLC=Non-small Cell Lung Cancer; RECIST v1.1=Response Evaluation Criteria in Solid Tumors v1.1; SMARCA2=SWI/SNF-Related, Matrix-Associated, Actin-Dependent Regulator of Chromatin, Subfamily A, Member 2; SMARCA4=SWI/SNF-Related, Matrix-Associated, Actin-Dependent Regulator of Chromatin, Subfamily A, Member 4; SWI/SNF=SWItch/Sucrose Non-Fermentable.

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Pipeline information is current through August 22, 2024.