LY4066434

PAN-KRAS INHIBITOR

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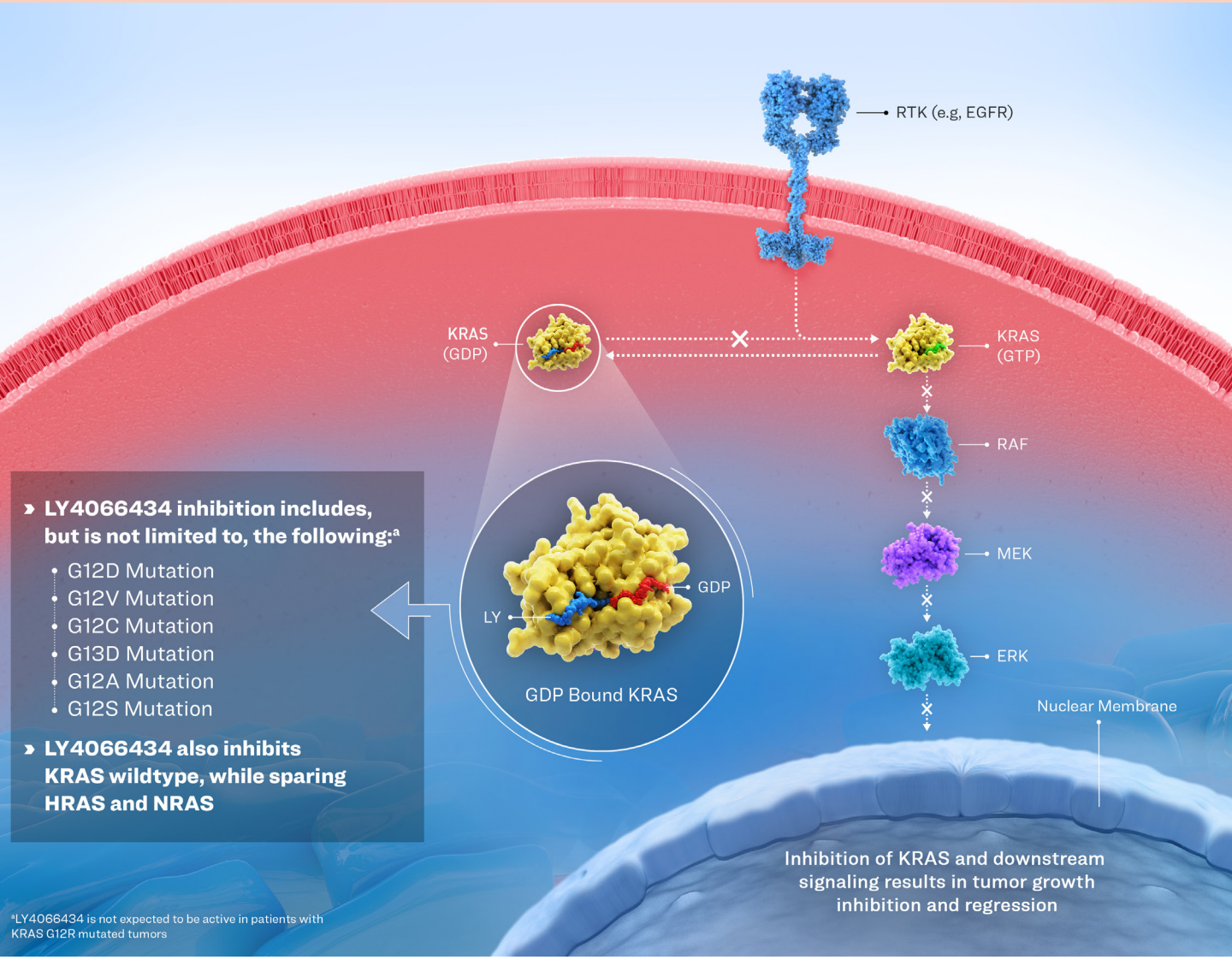
LY4066434 PAN-KRAS INHIBITOR
MECHANISM OF ACTION[1-4]



Kano Y, et al[1], Hofmann MH, et al[2], Ostrem JML, et al[3], Prieto Vallejo L, et al[4]

Abbreviations: EGFR=Epidermal Growth Factor Receptor; ERK=Extracellular Signal-Regulated kinases; G12A=Glycine at Position 12 Mutates to Alanine; G12C=Glycine at Position 12 Mutates to Cysteine; G12D=Glycine at Position 12 Mutates to Aspartate; G13D; Glycine at Position 13 Mutates to Aspartate; G12R=Glycine at Position 12 Mutates to Arginine; G12S=Glycine at Position 12 Mutates to Serine; G12V= Glycine at Position 12 Mutates to Valine; GDP=Guanosine Diphosphate; GTP=Guanosine Triphosphate; HRAS=Harvey Rat Sarcoma Virus; KRAS=Kirsten Rat Sarcoma Virus; LY=LY4066434; MEK=Mitogen Activated Protein Kinase; NRAS=Neuroblastoma RAS Viral Oncogene Homolog; RAF=Rapidly Accelerated Fibrosarcoma; RTK=Receptor Tyrosine Kinase.

References: 1. Kano Y, et al. *Nat Commun.* 2019;10(1):224. 2. Hofmann MH, et al. *Cancer Discov.* 2022;12(4):924-937. 3. Ostrem JML, et al. *Nat Rev Drug Discov.* 2016;15(11):771-785. 4. Prieto Vallejo L, et al. Poster presented at: *AACR* 2023. Abstract B116.

LY4066434 PAN-KRAS INHIBITOR

TARGET

KRAS is among the most frequently mutated oncogenes with multiple subtypes conferring a worse clinical prognosis.[1-3] While KRAS G12C inhibitors have received regulatory approval in certain countries, a significant unmet need persists for other *KRAS* mutant alleles, such as *KRAS* G12D, G12V, and G13D, which account for over 100,000 annual diagnoses in the United States alone.[3] Additionally, there are no selective targeted agents in clinical development for several less common *KRAS* mutations such as G12A and G12S.

MOLECULE

LY4066434 is an oral, non-covalent, pan-KRAS inhibitor.[4] In preclinical studies, scientists have observed that LY4066434 inhibition includes, but is not limited to, *KRAS* G12D, G12V, G12C, G13D, G12A, and G12S. Inhibition also includes wild-type KRAS, while sparing HRAS and NRAS.[3]

CLINICAL DEVELOPMENT

LY4066434 is being studied in patients with pancreatic cancer, colorectal cancer, non-small cell lung cancer, and other solid tumors who have qualifying *KRAS* mutations.

Abbreviations: G12A=Glycine at Position 12 Mutates to Alanine; G12C=Glycine at Position 12 Mutates to Cysteine; G12D=Glycine at Position 12 Mutates to Aspartate; G13D; Glycine at Position 13 Mutates to Aspartate; G12R=Glycine at Position 12 Mutates to Arginine; G12S=Glycine at Position 12 Mutates to Serine; G12V= Glycine at Position 12 Mutates to Valine; HRAS=Harvey Rat Sarcoma Virus; *KRAS*=Kirsten Rat Sarcoma Virus Gene; NRAS=Neuroblastoma RAS Viral Oncogene Homolog.

References: 1. Kim D, et al. *Nature.* 2023;619:160-166. 2. Zhu G, et al. *Mol Cancer.* 2021;20(1):143. 3. Hofmann MH, et al. *Cancer Discov.* 2022;12(4):924-937. 4. Prieto Vallejo L, et al. Poster presented at: *AACR* 2023. Abstract B116.

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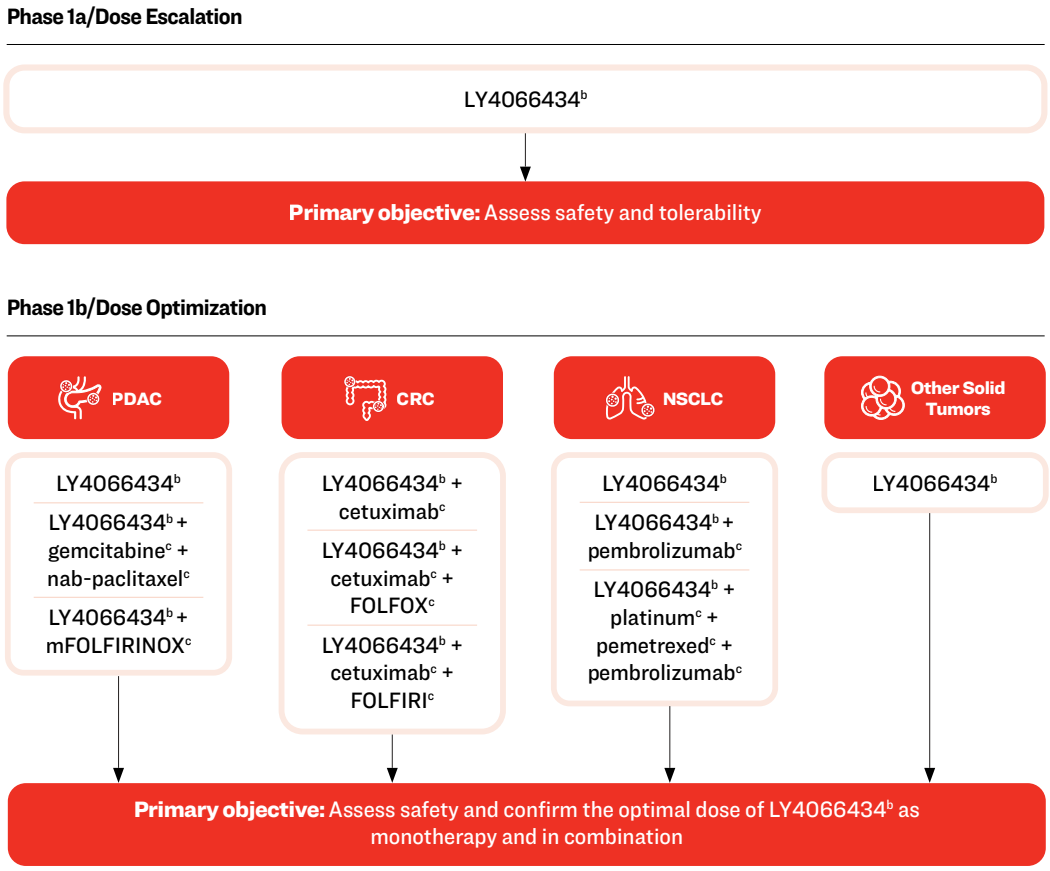
LY4066434 PAN-KRAS INHIBITOR

NCT06607185

A Phase 1a/1b Study of the Pan-KRAS Inhibitor LY4066434 in Participants With *KRAS* Mutant Solid Tumors[a]



[a]This clinical trial is currently being conducted in the USA and Japan. [b]Administered orally. [c]Administered intravenously.

Abbreviations: CRC=Colorectal Cancer; FOLFIRI=Fluorouracil, Leucovorin, and Irinotecan; FOLFOX=Fluorouracil, Leucovorin, and Oxaliplatin; *KRAS*=Kirsten Rat Sarcoma Virus Gene; mFOLFIRINOX=Fluorouracil, Leucovorin, Irinotecan, and Oxaliplatin; NSCLC=Non-small Cell Lung Cancer; PDAC=Pancreatic Ductal Adenocarcinoma.

Please visit clinicaltrials.gov for more information on this clinical trial [NCT06607185].

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NCT06607185

A Phase 1a/1b Study of the Pan-KRAS Inhibitor LY4066434 in Participants With *KRAS* Mutant Solid Tumors (Cont.)

KEY INCLUSION CRITERIA

- Histological or cytologically proven diagnosis of locally advanced, unresectable, and/or metastatic solid tumor cancer
- Have evidence of *KRAS* G12C, G12D, G12V, G12A, G12S, or G13D mutation in tumor tissue or circulating tumor DNA
- Have measurable disease per RECIST v1.1
- Have an ECOG performance status of ≤1
- Must be able to swallow tablets
- Select cohorts must have received ≥1 prior line of systemic chemotherapy for advanced or metastatic disease

KEY EXCLUSION CRITERIA

- Have known active CNS metastases and/or carcinomatous meningitis
  - Participants with asymptomatic or treated CNS disease may be eligible
- Have unresolved toxicities from prior therapy greater than NCI CTCAE v5.0 Grade 1 at the time of starting trial treatment, except for alopecia, peripheral neuropathy, and ongoing endocrinopathies controlled on appropriate replacement therapy
- Have significant cardiovascular disease defined as unstable angina or acute coronary syndrome, history of myocardial infarction, known reduced left ventricular ejection fraction or heart failure, uncontrolled or symptomatic arrhythmias
- Have known active hepatitis B, hepatitis C, or untreated HIV
- Have active uncontrolled systemic bacterial, viral, fungal, or parasitic infection
- Have other active malignancies unless in remission with life expectancy >2 years
- Have history of non-infectious pneumonitis/ILD that required steroids or has current clinically significant pneumonitis/ILD

Abbreviations: CNS=Central Nervous System; CTCAE v5.0=Common Terminology Criteria for Adverse Events Version 5.0; DNA=Deoxy-ribonucleic Acid; ECOG=Eastern Cooperative Oncology Group; ILD=Interstitial Lung Disease; *KRAS*=Kirsten Rat Sarcoma Virus Gene; NCI=National Cancer Institute; RECIST v1.1=Response Evaluation Criteria in Solid Tumors Version 1.1.

Please visit clinicaltrials.gov for more information on this clinical trial [NCT06607185].

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Pipeline information is current through October 11, 2024.