LY3537982

KRAS G12C INHIBITOR

LOXO @ Lilly

The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

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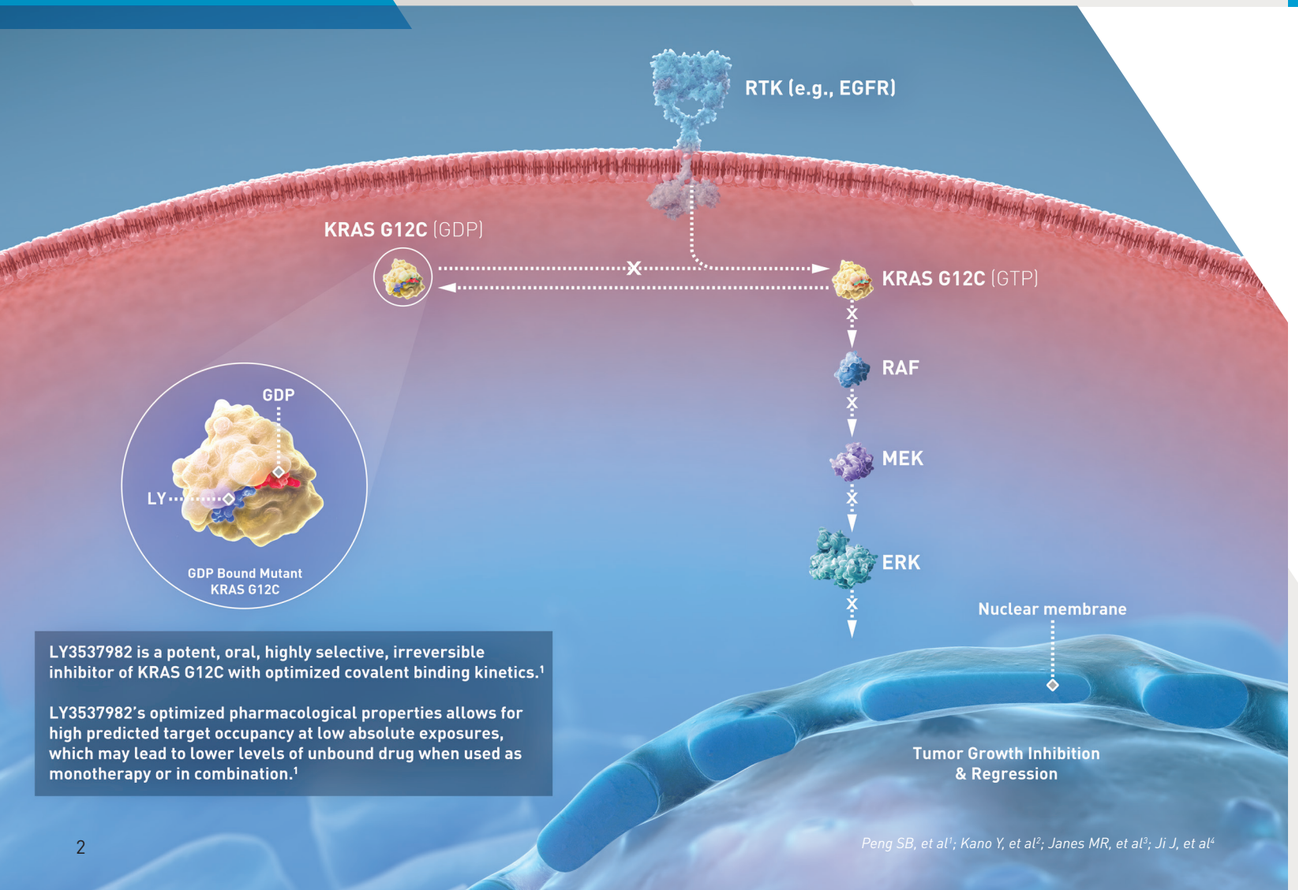

LY3537982 is a potent, oral, highly selective, irreversible inhibitor of KRAS G12C with optimized covalent binding kinetics.[1]

LY3537982's optimized pharmacological properties allows for high predicted target occupancy at low absolute exposures, which may lead to lower levels of unbound drug when used as monotherapy or in combination.[1]

Peng SB, et al[1]; Kano Y, et al[2]; Janes MR, et al[3]; Ji J, et al[4]

TARGET

KRAS is the most common oncogene across all tumor types. *KRAS G12C* represents a *KRAS* mutation in patients with non-small cell lung cancer (14%), colorectal cancer (3%), and other solid tumors (1%-3%).[4]

MOLECULE

LY3537982 is a selective covalent inhibitor of KRAS G12C; in preclinical models, it demonstrates activity as monotherapy and in combination with other anticancer therapies. It has competitive pharmacokinetic properties supporting its advancement into clinical testing. LY3537982 has been shown in vitro to target a *KRAS G12C* mutation, thereby inhibiting mutant KRAS-dependent signaling.[1]

CLINICAL DEVELOPMENT

LY3537982 is being studied in a clinical trial in patients with non-small cell lung cancer, colorectal cancer, or other advanced solid tumors.

References: 1. Peng SB, et al. *Cancer Res*. 2021;81(suppl 13):1259. **2.** Kano Y, et al. *Nat Commun*. 2019;10(1):224. **3.** Janes MR, et al. *Cell*. 2018;172(3):578-589. **4.** Ji J, et al. *Onco Targets Ther*. 2022;15:747-756.

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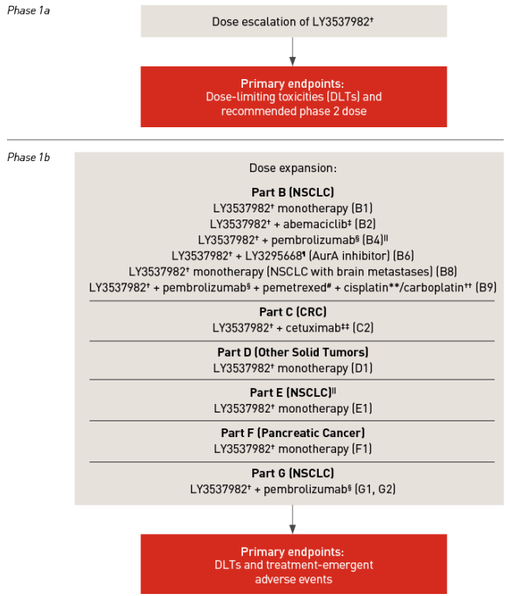
NCT04956640

A Phase 1a/1b Study of LY3537982 in Patients With *KRAS G12C*-Mutant Advanced Solid Tumors*



* This clinical trial is being conducted globally.
† LY3537982 is administered PO.
‡ Abemaciclib is administered PO.
§ Pembrolizumab is administered intravenously (IV).
|| Prior KRAS G12C inhibitor allowed.
¶ LY3295668 is administered PO.
# Pemetrexed is administered IV.
** Cisplatin is administered IV.
†† Carboplatin is administered IV.
‡‡ Cetuximab is administered IV.

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KEY INCLUSION CRITERIA

- Measurable disease as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)
- Evidence of *KRAS G12C* mutation in tumor tissue or circulating tumor DNA
- Histological or a cytologically proven diagnosis of locally advanced, unresectable, and/or metastatic cancer and meet cohort-specific criteria
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Adequate organ function
- Discontinued all previous treatments for cancer with resolution of any significant ongoing adverse events (AEs)
- Able to swallow capsules/tablets
- Must agree and adhere to contraceptive use, if applicable
- For some parts of the study (eg, one of the two arms with LY3537982 plus pembrolizumab and the arm of LY3537982 plus pembrolizumab, pemetrexed, and platinum therapy), histologically or cytologically confirmed stage IIIB-IIIC or stage IV NSCLC that is previously untreated in the advanced/metastatic setting and not suitable for curative intent radical surgery or radiation therapy. Previously untreated patients who received adjuvant and neoadjuvant therapy are eligible if the last dose of the systemic treatment was completed at least 6 months prior to enrollment. For untreated patients in the arm with LY3537982 plus pembrolizumab noted above, a single cycle of pembrolizumab may be initiated within 21 days prior to enrollment. For untreated patients in the arm of LY3537982 plus pembrolizumab, pemetrexed, and platinum therapy, a single cycle of the drugs other than LY3537982 may be initiated within 21 days prior to enrollment. Start of study treatment may be delayed to allow sufficient time for recovery from treatment-related toxicity

KEY EXCLUSION CRITERIA

- Disease suitable for local therapy administered with curative intent
- Active, ongoing, or untreated infection
- Serious preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study
- Serious cardiac conditions
- A second active primary malignancy or have been diagnosed and/or treated for an additional malignancy within 3 years prior to enrollment
- Symptomatic central nervous system (CNS) malignancy or metastasis and/or carcinomatous meningitis. Patients with treated CNS metastases are eligible for this study if their disease is asymptomatic, radiographically stable for at least 30 days, and they do not require treatment with steroids in the 2-week period prior to study treatment. This only applies to some parts of the study
- Prior treatment with any KRAS G12C small molecule inhibitor, except in certain scenarios where such prior therapy is allowed as per protocol
- Patients treated with drugs known to be strong inhibitors or inducers of cytochrome P450 (CYP)3A may be excluded
- The following patients will be excluded from some parts of the study:
  - Experienced certain serious side effects with prior immunotherapy
  - Have an active autoimmune disease that has required systemic anti-autoimmune treatment in the past 2 years
  - Have received a live vaccine within 30 days prior to the first dose of study drug
- Pregnant, breastfeeding, or expecting to conceive or father children within the projected duration of the trial through 180 days after the last dose of study medication
- Known allergic reaction against any of the components of the study treatments

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT04956640].

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ACTIVE TRIAL CURRENTLY NOT ENROLLING

[NCT06119581] Lung Cancer
SUNRAY-01: A Study of LY3537982 Plus Immunotherapy With or Without Chemotherapy in Participants With Non-Small Cell Lung Cancer (NSCLC) With a Change in a Gene Called KRAS G12C

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Pipeline information is current through November 2, 2023.
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