OLOMORASIB (LY3537982)

KRAS G12C INHIBITOR

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyloxooncologypipeline.com.

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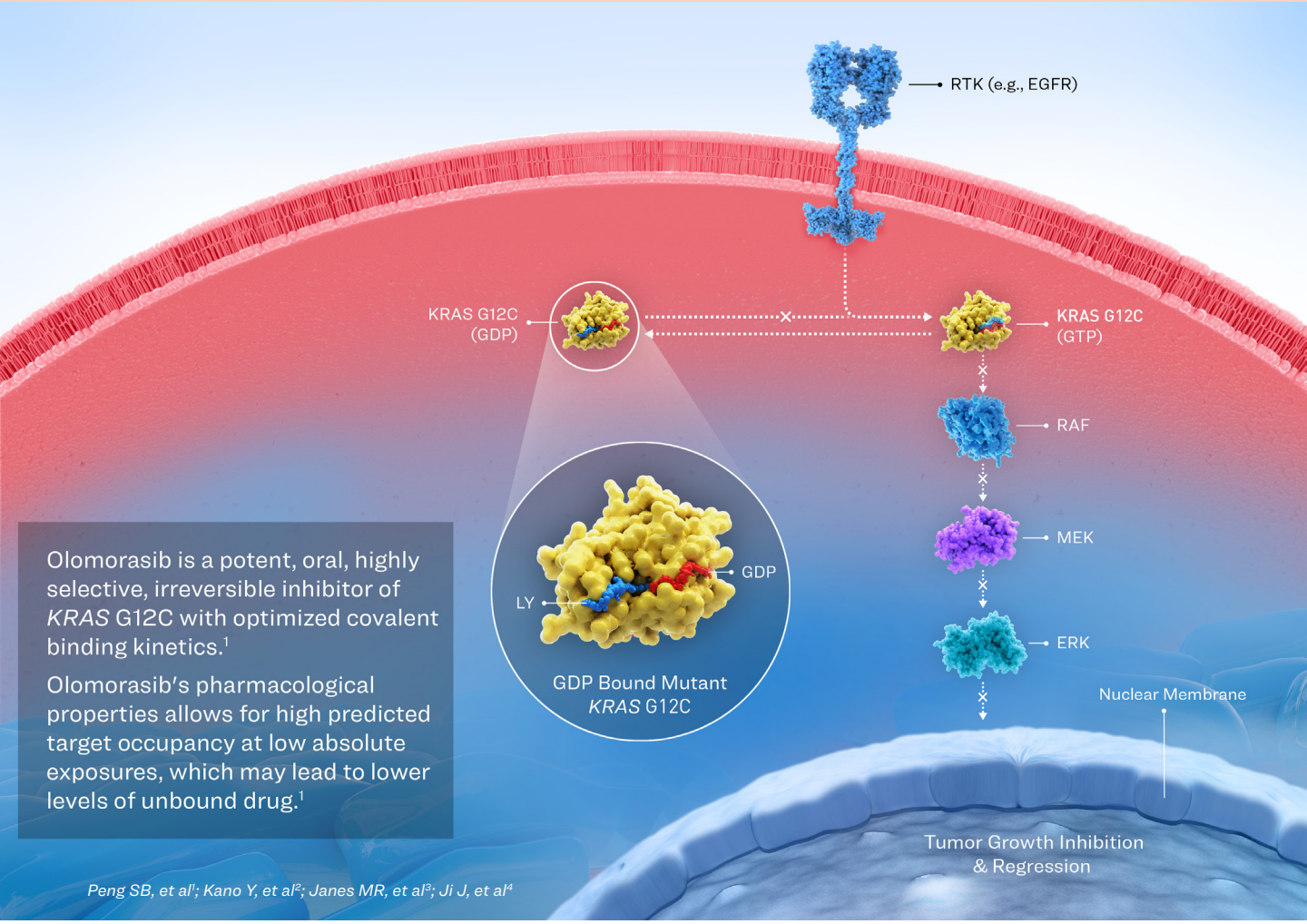
OLOMORASIB KRAS G12C INHIBITOR (LY3537982) | MECHANISM OF ACTION[1-4]



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

Olomorasib's pharmacological properties allows for high predicted target occupancy at low absolute exposures, which may lead to lower levels of unbound drug.[1]

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

Abbreviations: EGFR=Epidermal Growth Factor Receptor; ERK=Extracellular Signal-Regulated Kinase; GDP=Guanosine Diphosphate; GTP=Guanosine Triphosphate; KRAS=Kirsten Rat Sarcoma Viral Oncogene Homolog; LY=Olomorasib; MEK=Mitogen-Activated Extracellular Signal-Regulated Kinase; RAF=Rapidly Accelerated Fibrosarcoma; RTK=Receptor Tyrosine Kinase.

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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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%).[1]

MOLECULE

Olomorasib 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. Olomorasib has been shown *in vitro* to target a *KRAS* G12C mutation, thereby inhibiting mutant KRAS-dependent signaling.[2]

CLINICAL DEVELOPMENT

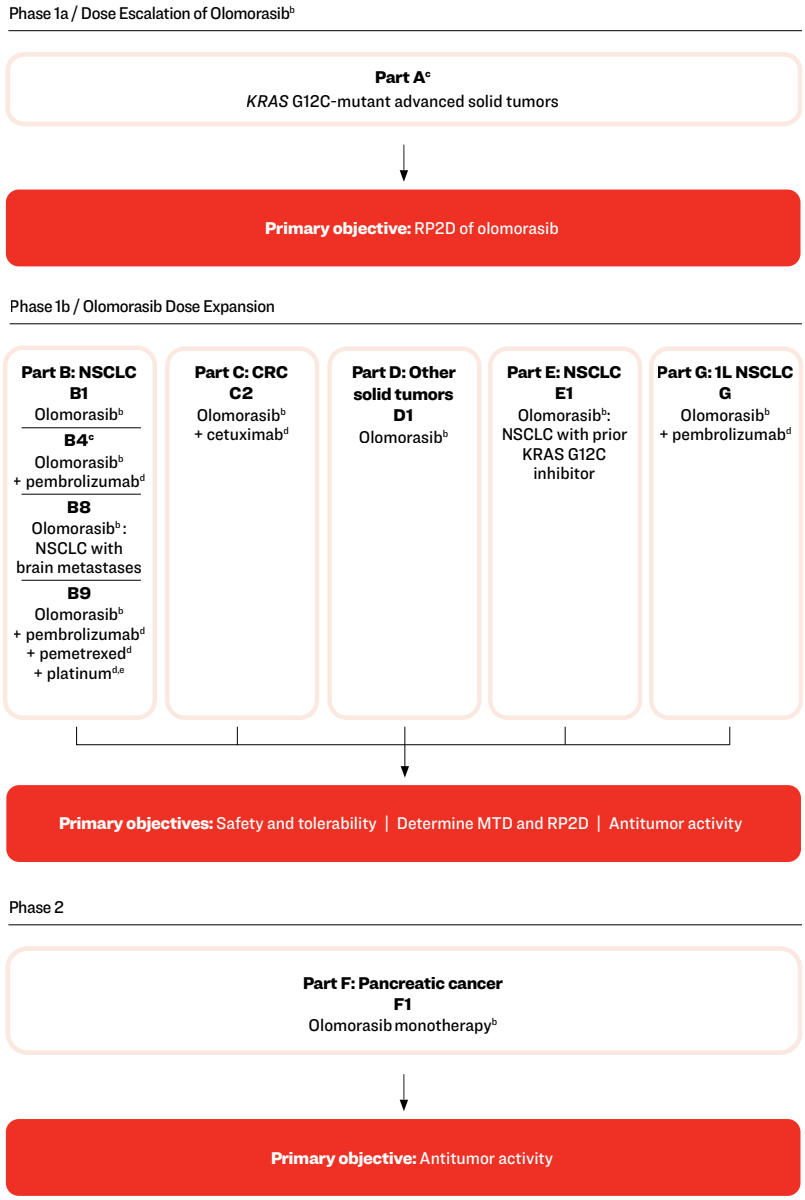
Olomorasib is being studied in a clinical trial in patients with non-small cell lung cancer, colorectal cancer, or other solid tumors.

References: 1. Ji J, et al. *Onco Targets Ther*. 2022;15:747-756. **2.** Peng SB, et al. *Cancer Res*. 2021;81(suppl 13):1259.

OLOMORASIB KRAS G12C INHIBITOR (LY3537982)

NCT04956640

A Phase 1/2 Study of LY3537982 in Patients With *KRAS* G12C-Mutant Advanced Solid Tumors[a]



a This clinical trial is being conducted globally; **b** Oral administration; **c** Prior KRAS G12C inhibitor allowed; **d** Intravenous administration; **e** platinum=cisplatin or carboplatin. **Abbreviations:** 1L=First-line of therapy; CRC=Colorectal Cancer; MTD=Maximum Tolerated Dose; NSCLC=Non-small-Cell Lung Cancer; RP2D=Recommended Phase 2 Dose. **Note:** Additional dose expansion cohorts in colon cancer and pancreatic cancer are not shown here.

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

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OLOMORASIB KRAS G12C INHIBITOR (LY3537982)

NCT04956640

A Phase 1/2 Study of LY3537982 in Patients With *KRAS* G12C-Mutant Advanced Solid Tumors[a] (cont.)

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), except in certain scenarios
- Able to swallow capsules/tablets
- Agree and adhere to contraceptive use, if applicable
- For some parts of the study (eg, one of the two arms with olomorasib plus pembrolizumab and the arm of olomorasib 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 olomorasib 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 olomorasib plus pembrolizumab, pemetrexed, and platinum therapy, a single cycle of any or all of the drugs other than olomorasib 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
- For one part of the study, participants must have received at least one prior oxaliplatin- or irinotecan-containing regimen for advanced or metastatic colorectal cancer (CRC)

KEY EXCLUSION CRITERIA

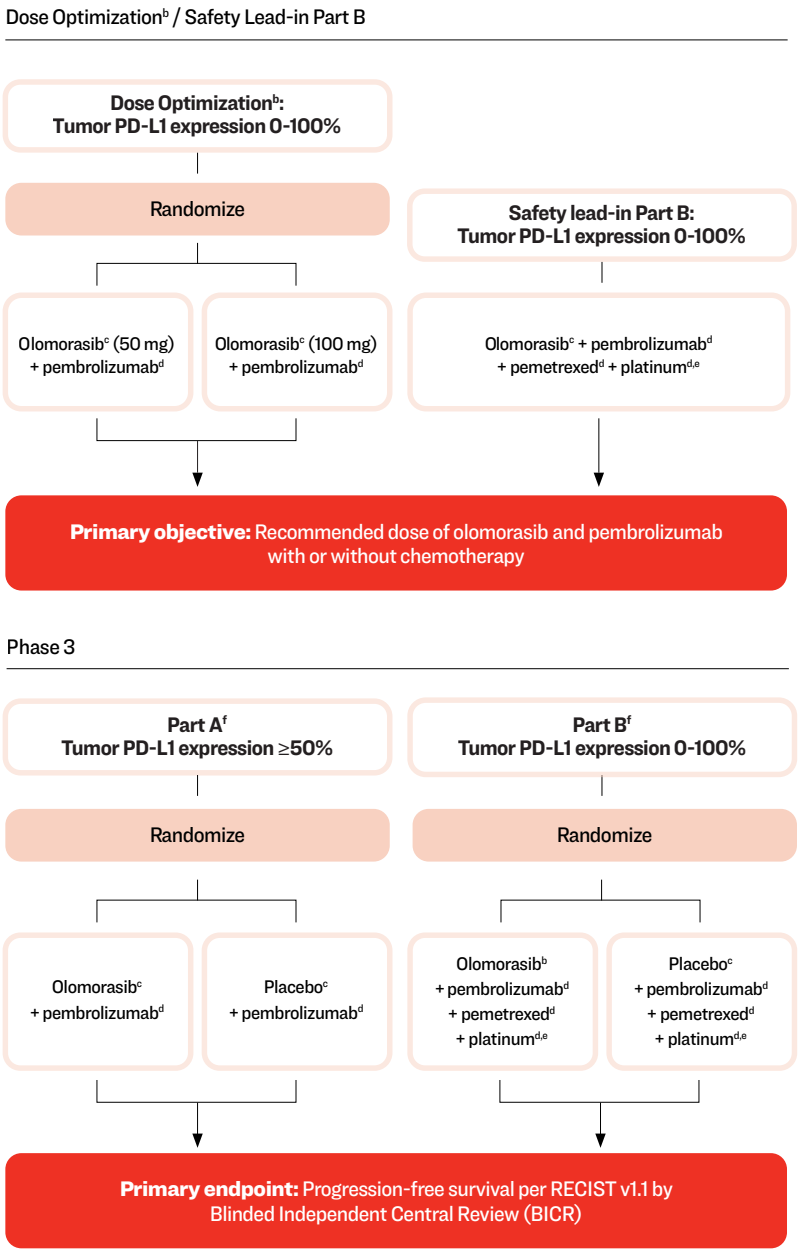
- Disease suitable for local therapy administered with curative intent
- Active, ongoing, or untreated infection
- Serious preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study
- Serious cardiac conditions
- A second active primary malignancy 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
- 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 clinicaltrials.gov for more information on this clinical trial [NCT04956640].

OLOMORASIB KRAS G12C INHIBITOR (LY3537982)

SUNRAY-01

A Global Pivotal Study in Participants With KRAS G12C-Mutant, Locally Advanced or Metastatic Non-Small Cell Lung Cancer Comparing First-Line Treatment of LY3537982 and Pembrolizumab vs Placebo and Pembrolizumab in Those With PD-L1 Expression ≥50% or LY3537982 and Pembrolizumab, Pemetrexed, Platinum vs Placebo and Pembrolizumab, Pemetrexed, Platinum Regardless of PD-L1 Expression[a]



a This clinical trial is being conducted globally; **b** Participants should be suitable for pembrolizumab monotherapy; **c** Oral administration; **d** Intravenous administration; **e** Platinum=cisplatin or carboplatin; **f** Participants with PD-L1 ≥50% are eligible to be enrolled to Part A or Part B at the discretion of the investigator. **Abbreviations:** BICR=Blinded Independent Central Review; PD-L1=Programmed Death-ligand 1; PFS=progression-free survival; R=Randomization; RECIST v1.1=Response Evaluation Criteria In Solid Tumors version 1.1.

Please visit clinicaltrials.gov for more information on this clinical trial [NCT06119581].

OLOMORASIB KRAS G12C INHIBITOR (LY3537982)

SUNRAY-01

A Global Pivotal Study in Participants With KRAS G12C-Mutant, Locally Advanced or Metastatic Non-Small Cell Lung Cancer Comparing First-Line Treatment of LY3537982 and Pembrolizumab vs Placebo and Pembrolizumab in Those With PD-L1 Expression ≥50% or LY3537982 and Pembrolizumab, Pemetrexed, Platinum vs Placebo and Pembrolizumab, Pemetrexed, Platinum Regardless of PD-L1 Expression[a] (cont.)

KEY INCLUSION CRITERIA

- Histologically or cytologically confirmed non-small cell lung cancer (NSCLC) with stage IIIB-IIIC or stage IV disease, not suitable for curative intent radical surgery or radiation therapy
- Part B and safety lead-in part B: the histology of the tumor must be predominantly non-squamous (in line with pemetrexed label)
- Disease with evidence of *KRAS* G12C mutation
- Known programmed death-ligand 1 (PD-L1) expression
  - Part A: ≥50%
  - Part B: 0%-100%
- Measurable disease as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Estimated life expectancy ≥12 weeks
- Ability to swallow capsules
- Adequate laboratory parameters
- Contraceptive use should be consistent with local regulations for those participating in clinical studies
- Women of childbearing potential must:
  - Have a negative pregnancy test
  - Not be breastfeeding during treatment and after study intervention for at least 180 days

KEY EXCLUSION CRITERIA

- A documented additional validated targetable oncogenic driver mutation or alteration in genes such as epidermal growth factor receptor *(EGFR)*, anaplastic lymphoma kinase *(ALK)*, *BRAF* (V600E), human epidermal growth factor receptor 2 (HER2), *MET* (exon 14), *ROS1*, rearranged during transfection *(RET)*, or neurotrophic tyrosine receptor kinase *(NTRK)*1/2/3
- Had any of the following prior to randomization:
  - Prior systemic therapy (chemotherapy, immunotherapy, targeted therapy, or biological therapy) for advanced or metastatic NSCLC
  - One cycle of standard-of-care treatment prior to study enrollment will be allowed for cases where immediate treatment is clinically indicated
- Central nervous system (CNS) metastases and/or carcinomatous meningitis
- For participants receiving pemetrexed and platinum (part B and safety lead-in part B):
  - Squamous cell and/or mixed small cell/non-small cell histology is not permitted
  - Is unable to interrupt aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Is unable or unwilling to take folic acid or vitamin B12 supplementation

Please visit clinicaltrials.gov for more information on this clinical trial [NCT06119581].

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

Pipeline information is current through June 12, 2024.