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.

### Key Inclusion Criteria
- Metastatic adenocarcinoma of the prostate
- Prostate cancer progression documented by prostate-specific antigen and/or radiographic progression as defined by Prostate Cancer Working Group 2 (PCWG2)
- Prior abiraterone treatment completed
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Adequate organ function
- Availability of tumor tissue

### Key Exclusion Criteria
- Prior treatment with a cytotoxic chemotherapy, a PI3K/AKT/mTOR agent, immune checkpoint inhibitors (eg, inhibitors of CTLA4, PD-1, PD-L1), investigational new generation potent anti-androgen therapy (eg, ARN 509), or enzalutamide. Participants may have received docetaxel in the hormone-sensitive setting
- History of seizure or any condition that may predispose to seizure
- Loss of consciousness or transient ischemic attack within 12 months
- Uncontrolled hypertension
- Insulin-dependent diabetes mellitus. Participants with type 2 diabetes mellitus are eligible if adequate control of blood glucose level is obtained by oral antidiabetics as documented by hemoglobin A1c <7%

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02407054].

* This clinical trial is being conducted in the United States in partnership with SCRI Development Innovations, LLC.
A Phase 1 First-in-Human Dose Study of LY3023414 in Patients With Advanced Cancer*

Key Inclusion Criteria
- Advanced and/or metastatic cancer (solid tumor or lymphoma)
- Measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or Revised Response Criteria for Malignant Lymphoma
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Life expectancy of >6 months
- Parts B2, B3, and B6: Tumor tissue available

LY3023414 dose based on part A.

Dose escalation in participants with advanced/metastatic cancer (including lymphoma)*
Part A1: LY3023414 orally once daily
Part A2: LY3023414 orally twice daily

Part B1†: LY3023414 + midazolam for drug-drug interaction (advanced/metastatic cancer)
Part B2†: LY3023414 + fulvestrant (advanced/metastatic breast cancer)
Part B3†: LY3023414 (malignant mesothelioma)
Part B4†: LY3023414 + pemetrexed/cisplatin (malignant mesothelioma)
Part B6†: LY3023414 (squamous non-small cell lung cancer characterized with PI3K activation)

Key Exclusion Criteria
- Serious preexisting medical conditions
- Symptomatic central nervous system malignancy
- Part B1 only: No concomitant medications that are strong inhibitors or inducers of CYP3A4 or midazolam
- Insulin-dependent diabetes mellitus or a history of gestational diabetes mellitus

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT01655225].

* This clinical trial is being conducted globally.

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**Target**

The PI3K/mTOR (phosphoinositide 3-kinase/mammalian target of rapamycin) pathway is stimulated by a variety of growth factors and their receptors and regulates cell metabolism, cell growth, cell survival, cell proliferation, cell motility, and angiogenesis. The PI3K/AKT/mTOR pathway is thought to be one of the most frequently mutated pathways in cancer,\(^1\,2\) leading to cancer progression and resistance to existing treatments.\(^2\,3\)

**Molecule**

LY3023414 is a selective inhibitor of class I PI3K isoforms, mTOR, and DNA-PK. Inhibition of PI3K/mTOR signaling by LY3023414 causes G1 cell-cycle arrest and results in broad antiproliferative activity in cancer cell panel screens. In vivo, LY3023414 demonstrates high bioavailability with dose-dependent target engagement and exhibits potent in vivo antitumor efficacy via intermittent target inhibition.\(^1\,4\)

**Clinical Development**

LY3023414 is being investigated in clinical trials in patients with non-small cell lung cancer and prostate cancer, including a combination therapy trial, and in phase I clinical trials, including a multi-cohort combination therapy trial.

**Study Schemas Not Available**

- [NCT02536586] Early Development  A Study of LY3023414 in Japanese Participants With Advanced Cancer
- [NCT02443337] Lung Cancer  A Study of LY3023414 and Necitumumab in Squamous Lung Cancer

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.

**References:**