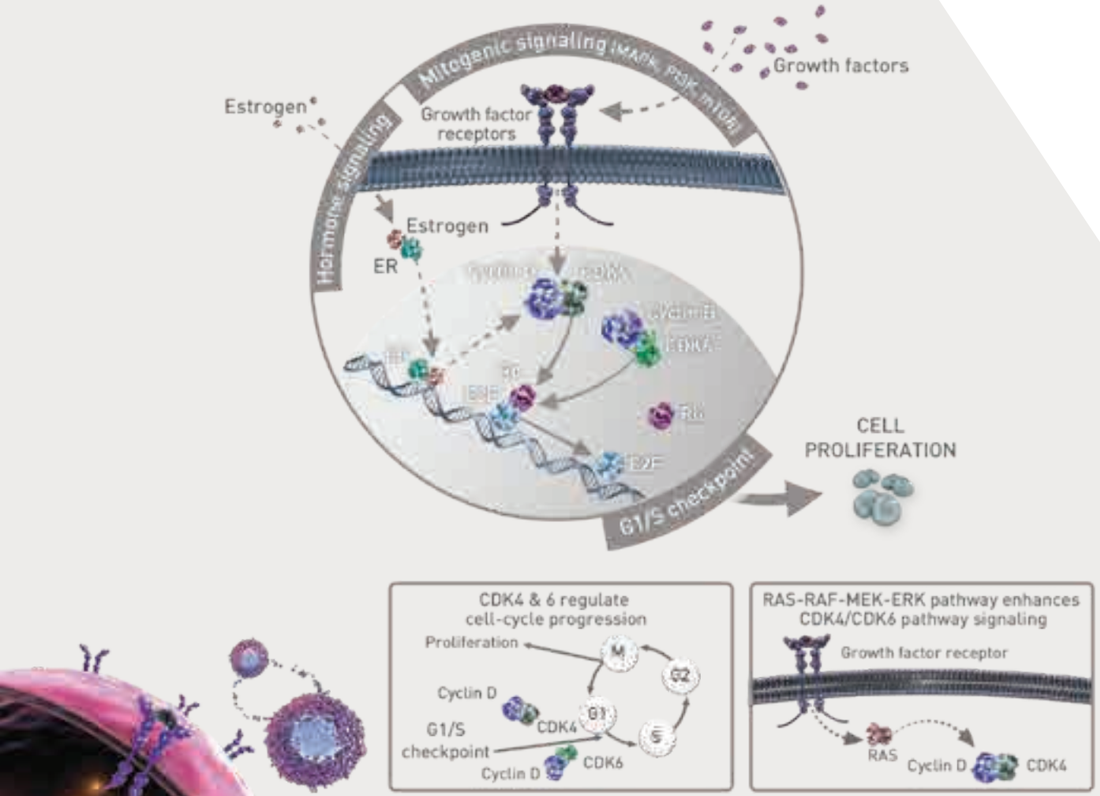
ABEMACICLIB

CDK4 & 6 INHIBITOR

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.



Shapiro GI[1]

TARGET

Many human tumors acquire alterations which can lead to the activation of cyclin-dependent kinases (CDKs). These alterations include mutations that directly activate CDK4 & 6 gene amplifications, which increase expression of various protein activators such as D-type cyclins; as well as genetic losses, which reduce expression of protein inhibitors such as p16. These various mechanisms as well as loss of retinoblastoma (Rb) can lead to an enhanced proliferative potential by decreasing dependency on external growth factors and mitogenic signaling pathways, which are required to stimulate growth under normal conditions.[2,3]

MOLECULE

Abemaciclib has been shown in vitro to be a selective ATP-competitive inhibitor of CDK4 & 6 kinase activity that prevents the phosphorylation and subsequent inactivation of the Rb tumor suppressor protein, thereby inducing G1 cell-cycle arrest and inhibition of cell proliferation.[4,5]

CLINICAL DEVELOPMENT

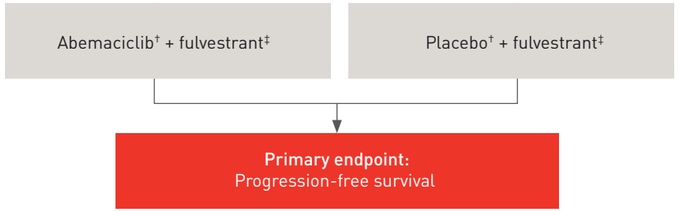
Abemaciclib is being investigated in clinical trials in patients with breast cancer, pediatric cancer, or prostate cancer.

References: 1. Shapiro GI. *J Clin Oncol.* 2006;24(11):1770-1783. **2.** Kim JK, Diehl JA. *J Cell Physiol.* 2009;220(2):292-296. **3.** Choi YJ, Anders L. *Oncogene.* 2014;33(15):1890-1903. **4.** Dempsey JA, et al. AACR Annual Meeting; April 6-10, 2013; Washington, DC. Abstract LB122. **5.** Gelbert LM, et al. *Invest New Drugs.* 2014;32(5):825-837.

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.

postMONARCH

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Compare the Efficacy of Abemaciclib Plus Fulvestrant to Placebo Plus Fulvestrant in Participants With HR+, HER2-, Advanced or Metastatic Breast Cancer Following Progression on a CDK4 & 6 Inhibitor and Endocrine Therapy*



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.

* This clinical trial is being conducted globally.
† Abemaciclib or placebo equivalent is administered PO.
‡ Fulvestrant is administered intramuscularly.

KEY INCLUSION CRITERIA

- Hormone-receptor-positive (HR+), HER2-negative (HER2-) locally advanced or metastatic breast cancer
- Radiologic evidence of disease progression or recurrence either:
  - On treatment with a CDK4 & 6 inhibitor with aromatase inhibitor (AI) as initial therapy for advanced disease, or
  - On/after treatment with a CDK4 & 6 inhibitor plus endocrine therapy (ET) administered as adjuvant therapy for early-stage breast cancer
- Must be deemed appropriate for treatment with ET
- If female, have a postmenopausal status by natural or surgical means or by ovarian function suppression
- Measurable disease and/or nonmeasurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Adequate renal, hematologic, and hepatic organ function
- Able to swallow capsules/tablets

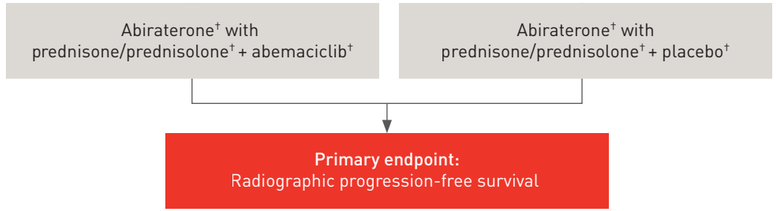
KEY EXCLUSION CRITERIA

- Visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis
- Symptomatic or untreated central nervous system metastasis
- Received any systemic therapy between disease recurrence/progression and study screening
- Received more than one line of therapy for advanced or metastatic disease
- Prior chemotherapy for metastatic breast cancer (MBC)
- Prior treatment with fulvestrant, any investigational estrogen receptor (ER)-directed therapy (including selective ER degraders (SERDs) and non-SERDs), any PI3K, mTOR, or AKT inhibitor

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT05169567].

CYCLONE 2

A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study of Abiraterone Acetate Plus Prednisone With or Without Abemaciclib in Patients With Metastatic Castration-Resistant Prostate 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.

* This clinical trial is being conducted globally.

† Abiraterone, prednisone (or prednisolone), and abemaciclib or placebo equivalent are administered PO.

KEY INCLUSION CRITERIA

- Metastatic prostate cancer documented by positive bone scan and/or measurable soft tissue metastatic lesions by computerized tomography (CT) or magnetic resonance imaging (MRI)
- Progressive disease at study entry demonstrated during continuous androgen-deprivation therapy (ADT)/post orchiectomy defined as one or more of the following:
  - Prostate-specific antigen (PSA) progression
  - Radiographic progression per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 for soft tissue and/or per Prostate Cancer Working Group 3 (PCWG3) for bone, with or without PSA progression
- Adequate organ function
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

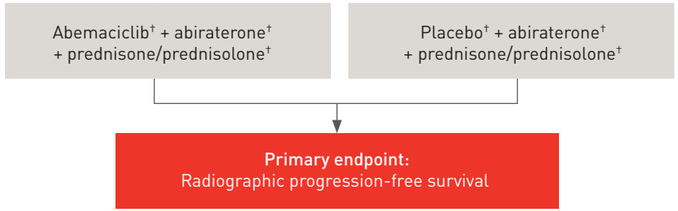
KEY EXCLUSION CRITERIA

- Prior therapy with CYP17 inhibitors
- Prior treatment with abemaciclib or any cyclin-dependent kinase (CDK) 4 & 6 inhibitors
- Prior cytotoxic chemotherapy for metastatic castration-resistant prostate cancer (participants treated with docetaxel for metastatic hormone-sensitive prostate cancer [mHSPC] are eligible). Prior radiopharmaceuticals for prostate cancer, or prior enzalutamide, apalutamide, darolutamide, or sipuleucel-T. Participants who had prior radiation or surgery to all target lesions
- Currently enrolled in a clinical study involving an investigational product
- Gastrointestinal disorder affecting the absorption or ability to swallow large pills
- Clinically significant heart disease, active or chronic liver disease, moderate/severe hepatic impairment (Child-Pugh Class B and C)

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT03706365].

CYCLONE 3

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Abemaciclib in Combination With Abiraterone Plus Prednisone in Men With High-Risk Metastatic Hormone-Sensitive Prostate 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.

* This clinical trial is being conducted globally.

† Abiraterone, prednisone (or prednisolone), and abemaciclib or placebo equivalent are administered PO.

KEY INCLUSION CRITERIA

- Adenocarcinoma of the prostate
- High-risk metastatic disease defined as ≥4 bone metastases and/or ≥1 visceral metastases
- Androgen deprivation therapy (either medical with a luteinizing hormone-releasing hormone [LHRH] analogue or surgical castration) must have been started prior to randomization and continued throughout the study
- Adequate organ function
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

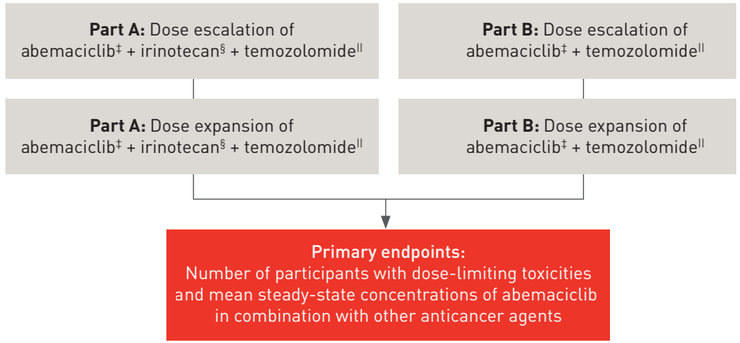
KEY EXCLUSION CRITERIA

- Prior treatment with abemaciclib or any other cyclin dependent kinase 4 and 6 (CDK4 & 6) inhibitor
- Development of metastatic prostate cancer in the context of castrate levels of testosterone (≤50 ng/dL)
- Received any prior systemic therapy for metastatic prostate cancer (including investigational agents); the following exceptions are permitted:
  - Up to 3 months of androgen deprivation therapy (ADT) (when given without docetaxel) AND absence of radiographic or prostate specific antigen (PSA) progression prior to randomization
  - Up to 6 cycles of docetaxel with ADT AND absence of radiographic or PSA progression prior to randomization
- Clinically significant cardiovascular disease as evidenced by myocardial infarction, arterial thrombotic events, or severe/unstable angina in the past 6 months, or New York Heart Association Class II to IV heart failure
- History of syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin, or sudden cardiac arrest. Chronic and hemodynamically stable atrial arrhythmia well-controlled on medical therapy is permitted
- Uncontrolled hypertension
- Clinically active or chronic liver disease, moderate/severe hepatic impairment
- Known untreated central nervous system (CNS) metastasis. Patients with a history of treated brain metastases are eligible provided that disease is stable following treatment for at least 8 weeks prior to randomization and no requirement for corticosteroid use

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT05288166].

NCT04238819

A Phase 1b Dose Escalation Study of Abemaciclib in Combination With Temozolomide and Irinotecan (Part A) and Abemaciclib in Combination With Temozolomide (Part B) in Pediatric and Young Adult Patients With Relapsed/Refractory Solid Tumors*†



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.

* This clinical trial is being conducted globally.
† Additional criteria not shown here may exist for individual parts of the study.
‡ Abemaciclib is administered PO.
§ Irinotecan is administered intravenously.
|| Temozolomide is administered PO.

KEY INCLUSION CRITERIA

- ≤18 years of age at the time of study enrollment
- Body weight ≥10 kg and body surface area ≥0.5 m^2
- Any relapsed/refractory malignant solid tumor (excluding lymphoma), including central nervous system tumors, that have progressed on standard therapies and, in the judgment of the investigator, are appropriate candidates for the experimental therapy combinations in the study
- Lansky score ≥50 for participants ≤16 years of age, and Karnofsky score ≥50 for participants >16 years of age
- Discontinued all previous treatments for cancer or investigational agents and recovered from acute effects to grade ≤1 at the time of enrollment
- Able to swallow
- Adequate hematologic and organ function ≤14 days prior to first dose of study drug
- Females of reproductive potential must have negative serum pregnancy test at baseline within 7 days prior to starting treatment
- Both female and male participants of reproductive potential must agree to use highly effective contraceptive precautions (and avoid sperm donation for males) during the trial. For abemaciclib, females should use contraception for at least 3 weeks following the last abemaciclib dose (males have no restriction for contraceptive use following treatment with abemaciclib). For other study drugs, highly effective contraceptive precautions (and avoiding sperm donation) must be used according to their label
- Life expectancy of at least 8 weeks and able to complete at least one cycle of treatment
- Caregivers and participants willing to make themselves available for the duration of the trial

KEY EXCLUSION CRITERIA

- Tumor containing known somatic or germline Rb mutation (screening is not required for enrollment)
- Prior allogenic bone marrow or solid organ transplant
- Live vaccination within 4 weeks prior to starting study treatment
- History of syncope of cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest within the last 12 months
- Intolerability or hypersensitivity to any of the study treatments or its components
- Diagnosed and/or treated additional malignancy within 3 years prior to enrollment that may affect the interpretation of results, with the exception of curatively treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, and/or curatively resected in situ cervical and/or breast cancers
- Pregnant or breastfeeding
- Active systemic infections or viral load
- Serious and/or uncontrolled preexisting medical conditions that would preclude participation in this study
- Prior treatment with drugs known to be strong inhibitors or inducers of isoenzyme cytochrome P450 3A (CYP3A) or strong inhibitors of UGT1A1 if the treatment cannot be discontinued or switched to a different medication at least 5 half-lives prior to starting study drug
- Prior treatment with a CDK4 & 6 inhibitor
- Current enrollment in any other clinical study involving an investigational product or nonapproved use of a drug or device
- Prior experimental treatment in a clinical trial within the last 30 days or 5 half-lives, whichever is longer
- Part A only: Bowel obstruction

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT04238819].

ACTIVE TRIALS CURRENTLY NOT ENROLLING

[NCT02057133] Breast Cancer
A Study of LY2835219 (Abemaciclib) in Combination With Therapies for Breast Cancer That Has Spread

[NCT02107703] Breast Cancer
MONARCH 2: A Study of Abemaciclib (LY2835219) Combined With Fulvestrant in Women With Hormone-Receptor-Positive, HER2-Negative Breast Cancer

[NCT02246621] Breast Cancer
MONARCH 3: A Study of Nonsteroidal Aromatase Inhibitors Plus Abemaciclib (LY2835219) in Postmenopausal Women With Breast Cancer

[NCT02675231] Breast Cancer
monarcHER: A Study of Abemaciclib (LY2835219) in Women With HR+, HER2+ Locally Advanced or Metastatic Breast Cancer

[NCT02747004] Breast Cancer
Next MONARCH 1: A Study of Abemaciclib (LY2835219) Plus Tamoxifen or Abemaciclib Alone in Women With Metastatic Breast Cancer

[NCT02763566] Breast Cancer
MONARCH plus: A Study of Abemaciclib (LY2835219) in Participants With Breast Cancer

[NCT03155997] Breast Cancer
monarchE: Endocrine Therapy With or Without Abemaciclib (LY2835219) Following Surgery in Participants With Breast Cancer

[NCT03703466] Breast Cancer
A Study of Abemaciclib (LY2835219) With and Without Food in Participants With Metastatic Breast Cancer

[NCT04408924] Prostate Cancer
CYCLONE 1: A Study of Abemaciclib in Metastatic Castration-Resistant Prostate Cancer Patients

Lilly

Pipeline information is current through April 28, 2022.
VV-OTHR-US-DEL-0824 04/2022 PRINTED IN USA