ABEMACICLIB

CDK4 & 6 INHIBITOR

LOXO @ Lilly

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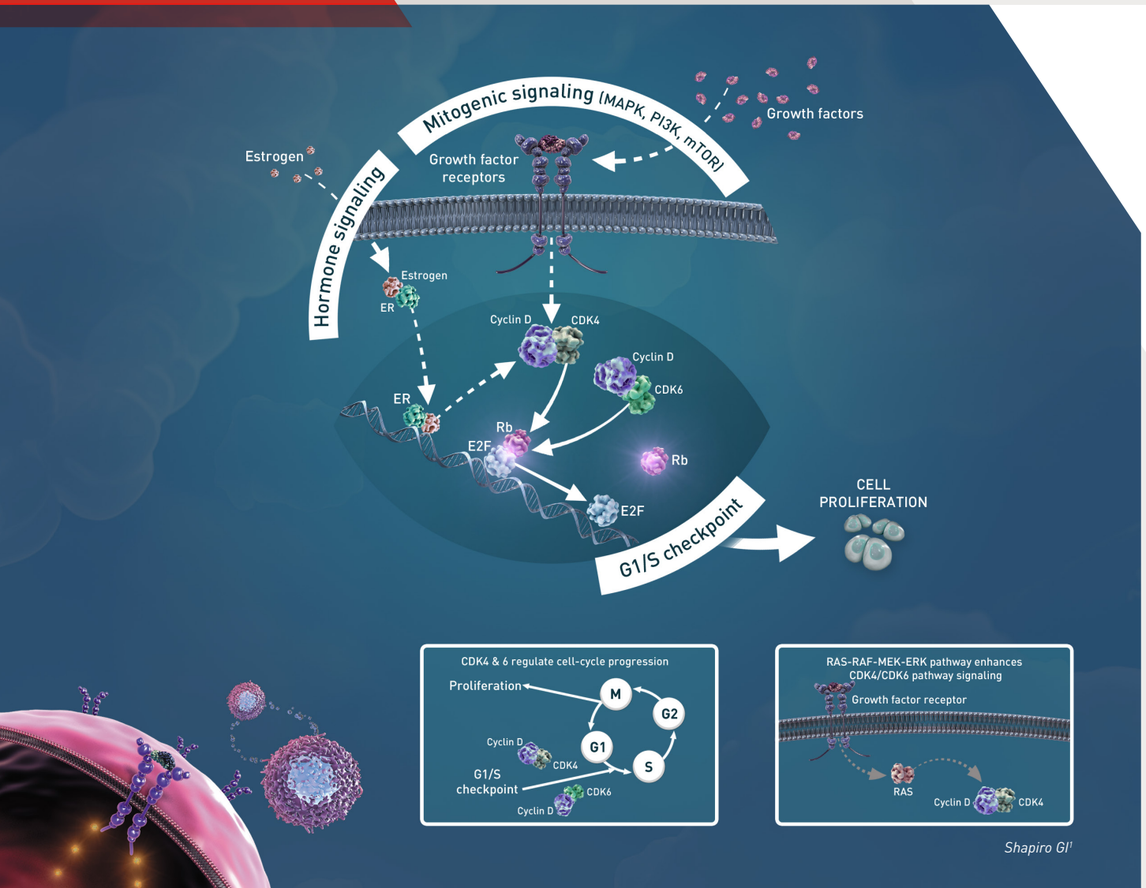

TARGET

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, non-small cell lung cancer, pediatric cancers, prostate cancer, or sarcoma.

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.

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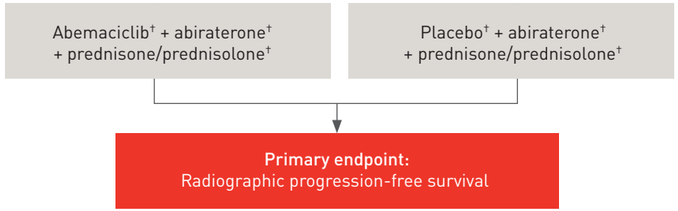
CYCLONE 3

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*



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* 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 (as the predominant histology)
- High-risk metastatic hormone-sensitive prostate cancer. High risk is defined as: ≥4 bone metastases by bone scan and/or ≥1 visceral metastases by CT or MRI
- Must have initiated androgen deprivation therapy (ADT) with luteinizing hormone-releasing hormone (LHRH) agonist/antagonist or bilateral orchiectomy prior to randomization. Up to 3 months of ADT prior to randomization is permitted with or without first-generation anti-androgen
- Adequate organ function
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

KEY EXCLUSION CRITERIA

- Prior treatment with abemaciclib or any other CDK4 & 6 inhibitor
- Development of metastatic prostate cancer in the context of castrate levels of testosterone
- Received any prior systemic therapy for metastatic prostate cancer (including investigational agents), except for ADT and first-generation anti-androgen
- 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 if stable for at least 8 weeks prior to randomization and off corticosteroid for at least 2 weeks prior to randomization

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

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NCT04238819

A Phase 1b/2 Study of Abemaciclib in Combination With Irinotecan and Temozolomide (Part A) and Abemaciclib in Combination With Temozolomide (Part B) in Pediatric and Young Adult Patients With Relapsed/Refractory Solid Tumors and Abemaciclib in Combination With Dinutuximab, GM-CSF, Irinotecan, and Temozolomide in Pediatric and Young Adult Patients With Relapsed/Refractory Neuroblastoma (Part C)*†

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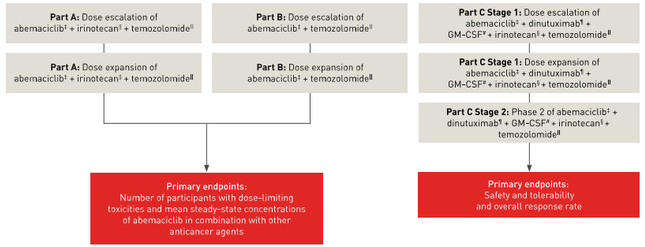

* This clinical trial is being conducted globally.
† Additional criteria not shown here may exist for individual parts of the study.
‡ Abemaciclib is administered PO.
§ Irinotecan is administered intravenously (IV).
|| Temozolomide is administered PO or IV.
¶ Dinutuximab is administered IV.
# GM-CSF is administered subcutaneously.

KEY INCLUSION CRITERIA

Parts A and B only:

- ≤18 years of age
- Body weight ≥10 kilograms and body surface area (BSA) ≥0.5 m^2
- Any relapsed/refractory malignant solid tumor (excluding lymphoma), including central nervous system tumors, that have progressed on standard therapies
- For parts B and C, participants with neuroblastoma who are eligible for part C will be excluded from part B unless approved by the investigator

Part C only:

- <21 years of age
- BSA ≥0.2 m^2
- First relapse/refractory neuroblastoma

All parts:

- Measurable or evaluable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or Response Assessment in Neuro-Oncology (RANO)
- A Lansky score ≥50 for participants <16 years of age or Karnofsky score ≥50 for participants ≥16 years of age
- Discontinued all previous treatments for cancer or investigational agents and recovered from the acute effects to grade ≤1 at the time of enrollment
- Able to swallow and/or have a gastric/nasogastric tube
- Adequate hematologic and organ function ≤2 weeks (14 days) prior to first dose of study treatment
- Females of reproductive potential must have negative urine or serum pregnancy test at baseline (within 7 days prior to starting treatment)
- Female participants of reproductive potential must agree to use highly effective contraceptive precautions during the trial. For abemaciclib, females should use contraception for at least 3 weeks following the last 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 1 cycle of treatment
- Caregivers and participants willing to make themselves available for the duration of the trial

KEY EXCLUSION CRITERIA

- Prior allogenic bone marrow or solid organ transplant
- Prior live vaccination
- 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
- Serious and/or uncontrolled preexisting medical condition(s)
- Parts A and C only: Bowel obstruction
- Prior treatment with drugs known to be strong inhibitors or inducers of isoenzyme cytochrome P450 3A (CYP3A) or strong inhibitors of uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1) if the treatment cannot be discontinued or switched to a different medication at least 5 half-lives prior to starting study treatment
- Prior treatment with cyclin-dependent kinase (CDK) 4 & 6 inhibitor
- Part C only: Received prior systemic therapy for relapsed/refractory neuroblastoma
- Part C only: Received prior anti-GD2 therapy during induction phase
- Currently enrolled in any other clinical study involving an investigational product or non-approved use of a drug or device
- Received an experimental treatment in a clinical trial within the last 30 days or 5 half-lives, whichever is longer

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

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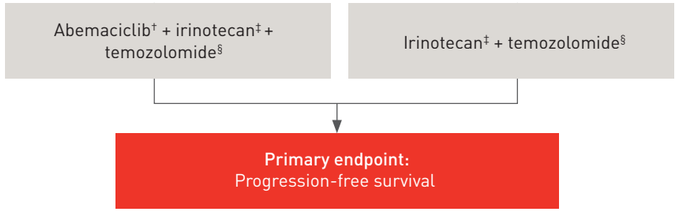
CAMPFIRE

A Randomized, Open-Label, Phase 2 Study Evaluating Abemaciclib in Combination With Irinotecan and Temozolomide in Participants With Relapsed or Refractory Ewing's Sarcoma*



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* This clinical trial is being conducted globally.
† Abemaciclib is administered PO.
‡ Irinotecan is administered intravenously.
§ Temozolomide is administered PO.

KEY INCLUSION CRITERIA

- Ages 1 to 39
- Ewing's sarcoma or Ewing's sarcoma-like tumor
  - The original pathological report is required; repeat biopsy at progression is not required
- Refractory disease or confirmed radiological progression or recurrence following first or later line of treatment of Ewing's sarcoma or Ewing's sarcoma-like tumor
  - Participants must have one measurable or evaluable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Lansky score ≥50 for participants <16 years of age, and Karnofsky score ≥50 for participants ≥16 years of age
- Participants must have discontinued all previous treatments for cancer or investigational agents ≥7 days after the last dose and must have recovered from the acute effects
- Adequate hematologic and organ function ≤14 days prior to day 1 of cycle 1
  - Platelets ≥75 x 10^9/L, hemoglobin ≥8 g/dL, and absolute neutrophil count ≥1.0 x 10^9/L
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0 × upper limit of normal (ULN); total bilirubin ≤1.5 × ULN
  - Creatinine clearance or calculated glomerular filtration rate (GFR) ≥60 mL/min/m^2 or serum creatinine based on age/gender
- Female participants of childbearing potential must have a negative urine or serum pregnancy test
- Body weight ≥10 kg
- Must be able to swallow and/or have a gastric/nasogastric tube
  - Participants in the European Union must be able to swallow intact capsules
- Stable or decreasing dose of steroids at least 7 days prior to enrollment
- Life expectancy of at least 8 weeks and able to complete at least 1 cycle of treatment

KEY EXCLUSION CRITERIA

- Participants/caregivers are willing to follow study procedures and make themselves available for the duration of the study
- Severe and/or uncontrolled concurrent medical disease or psychiatric illness/social situation that, in the judgment of the investigator, could cause unacceptable safety risks or compromise compliance with the protocol
- Active fungal, bacterial, and/or known severe viral infection, including but not limited to HIV or viral hepatitis A, B, or C
- Prior allogeneic bone marrow or solid organ transplant
- Major surgical procedure, laparoscopic procedure, or significant traumatic injury within 28 days prior to enrollment. Surgical or other wounds must be adequately healed prior to enrollment
- Pregnant or breastfeeding
- Prior treatment with a CDK4 & 6 inhibitor
- Progression during prior treatment with irinotecan and/or temozolomide
- Known intolerability or hypersensitivity to any of the study treatments or dacarbazine
- Diagnosed and/or treated for an additional malignancy within 3 years prior to enrollment

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT05440786].

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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

[NCT02779751] Lung Cancer or Breast Cancer
A Study of Abemaciclib (LY2835219) in Participants With Non-Small Cell Lung Cancer or 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

[NCT05169567] Breast Cancer
postMONARCH: Abemaciclib (LY2835219) Plus Fulvestrant Compared to Placebo Plus Fulvestrant in Previously Treated Breast Cancer

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

[NCT03706365] Prostate Cancer
CYCLONE 2: A Study of Abiraterone Acetate Plus Prednisone With or Without Abemaciclib (LY2835219) in Participants With Prostate Cancer

[NCT05999968] Prostate Cancer
Abemaciclib Plus Darolutamide in Prostate Cancer That Has Spread After Initial Treatment

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Pipeline information is current through November 2, 2023.

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