ABEMACICLIB (LY2835219)

CDK4/6 INHIBITOR

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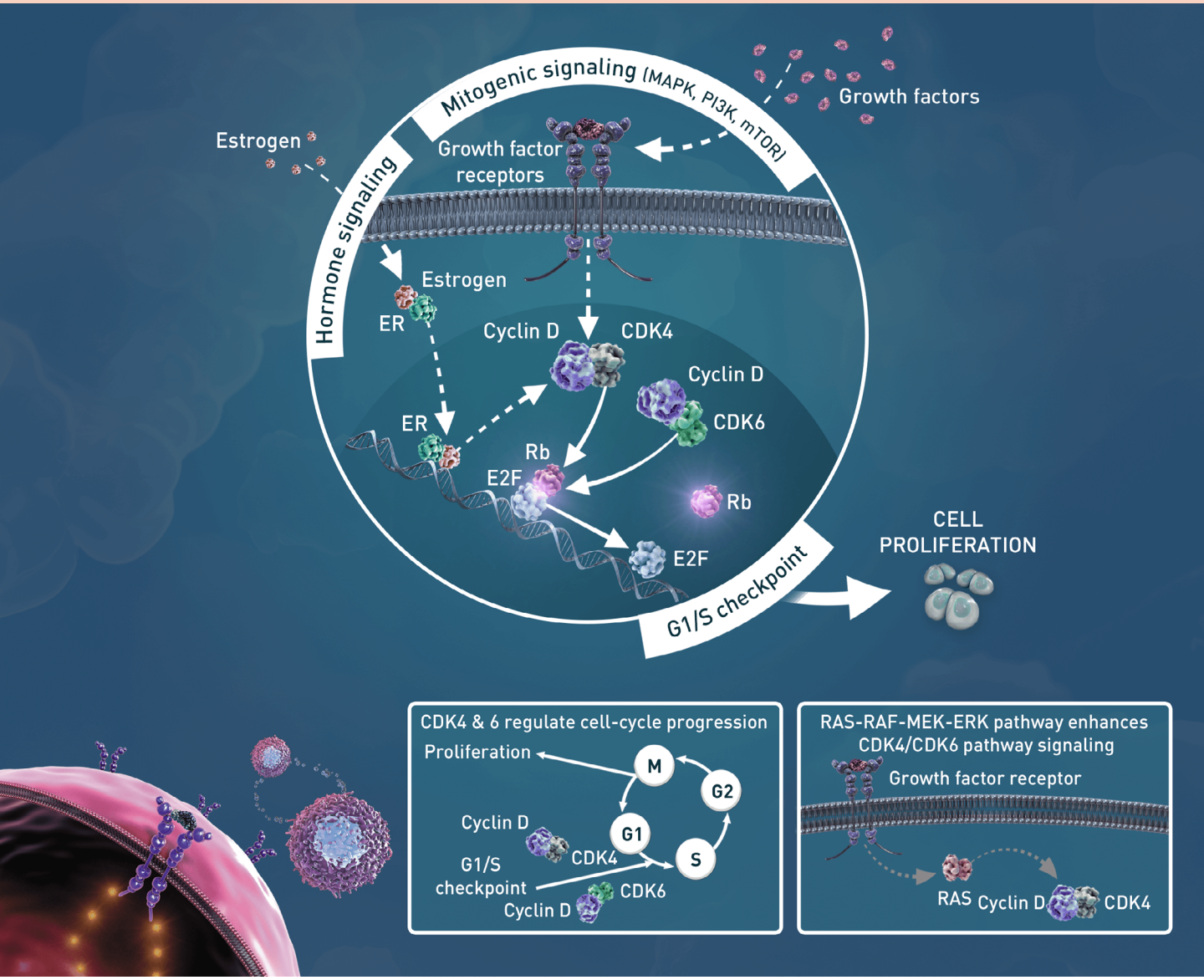
ABEMACICLIB CDK4/6 INHIBITOR (LY2835219) | MECHANISM OF ACTION[1]



Shapiro G

Reference: 1. Shapiro GI. *J Clin Oncol.* 2006;24(11):1770-1783.

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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.[1,2]

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.[3,4]

CLINICAL DEVELOPMENT

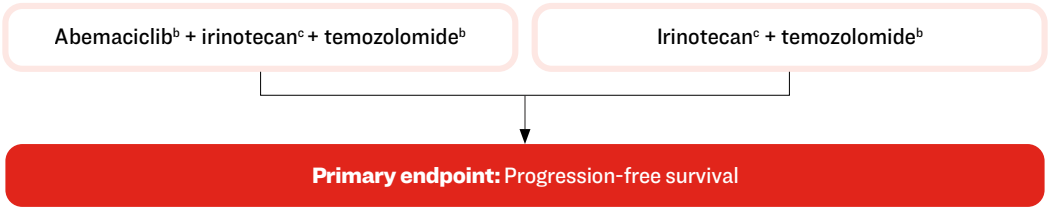
Abemaciclib is being investigated in clinical trials in patients with breast cancer, non-small cell lung cancer, pediatric cancers, or sarcoma.

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

ABEMACICLIB CDK4/6 INHIBITOR (LY2835219)

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[a]



[a]This clinical trial is being conducted globally. [b]Administered orally. [c]Administered intravenously.

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

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ABEMACICLIB CDK4/6 INHIBITOR (LY2835219)

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 (Cont.)

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 version 1.1 (RECIST v1.1)
- 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 ≥75,000/cubic millimeter (mm^3), hemoglobin ≥8 g/dL, and absolute neutrophil count ≥1000/microliter (μL)
  - 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
- Participants/caregivers are able and willing to make themselves available for the duration of the study and are willing to follow study procedures, including adherence to the pharmacokinetic (PK) sampling schedule

KEY EXCLUSION CRITERIA

- 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 cyclin-dependent kinase 4 and 6 (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 clinicaltrials.gov for more information on this clinical trial [NCT05440786].

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ACTIVE TRIALS CURRENTLY NOT ENROLLING

[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

[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

[NCT04238819] Solid Tumors
A Study of Abemaciclib (LY2835219) in Combination With Other Anti-Cancer Treatments in Children and Young Adult Participants With Solid Tumors, Including Neuroblastoma

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

[NCT02152631] Lung Cancer
JUNIPER: A Study of Abemaciclib (LY2835219) in Participants With Previously Treated *KRAS* Mutated Lung Cancer

[NCT05288166] Prostate Cancer
CYCLONE 3: A Study of Abemaciclib (LY2835219) With Abiraterone in Men With Prostate Cancer That Has Spread to Other Parts of the Body and is Expected to Respond to Hormonal Treatment (Metastatic Hormone-Sensitive Prostate Cancer)

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ACTIVE TRIALS CURRENTLY NOT ENROLLING (CONT.)

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

[NCT04975308] Breast Cancer
EMBER-3: A Study of Imlunestrant, Investigator's Choice of Endocrine Therapy, and Imlunestrant Plus Abemaciclib in Participants With ER+, HER2- Advanced Breast Cancer

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

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

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

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

[NCT02791334] Solid Tumors
PACT: A Study of Anti-PD-L1 Checkpoint Antibody (LY3300054) Alone and in Combination in Participants With Advanced Refractory Solid Tumors

[NCT04188548] Breast Cancer or Endometrial Cancer
EMBER: A Study of LY3484356 in Participants With Advanced or Metastatic Breast Cancer or Endometrial Cancer

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Pipeline information is current through July 27, 2024.