Development Program

August 2020

Pfizer Investigational Agents for Breast Cancer Now (BCN) Catalyst Program

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Development Program

August 2020

Crizotinib

ALK Inhibitor

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Overview

- Anaplastic lymphoma kinase (ALK) chromosomal translocations have been detected in several human malignancies including in anaplastic large cell lymphomas (ALCLs), neuroblastomas, and non-small cell lung cancer (NSCLC)
- Crizotinib is an inhibitor of receptor tyrosine kinases including ALK
- Translocations in the ALK gene cause the expression of oncogenic fusion proteins, which can activate and dysregulate the gene's expression and signaling, contributing to cell proliferation and survival in tumors expressing these proteins

Katayama R. Drug resistance in anaplastic lymphoma kinase-rearranged lung cancer. *Cancer Sci.* 2018;109:572-580. Pfizer Inc. XALKORI® (Crizotinib) US Prescribing Information.

Stage of Development

Crizotinib is being investigated as a single agent in the following tumor types. Crizotinib is not approved for the uses listed below.

Anaplastic Large Cell Lymphoma (ALCL) in Children & Adults; Inflammatory Myofibroblastic Tumor (IMT)	Phase 1b*

*Closed to enrollment.

ClinicalTrials.gov. Accessed August 3, 2020. http://clinicaltrials.gov/

Development Program

August 2020

Palbociclib

CDK 4/6 Inhibitor

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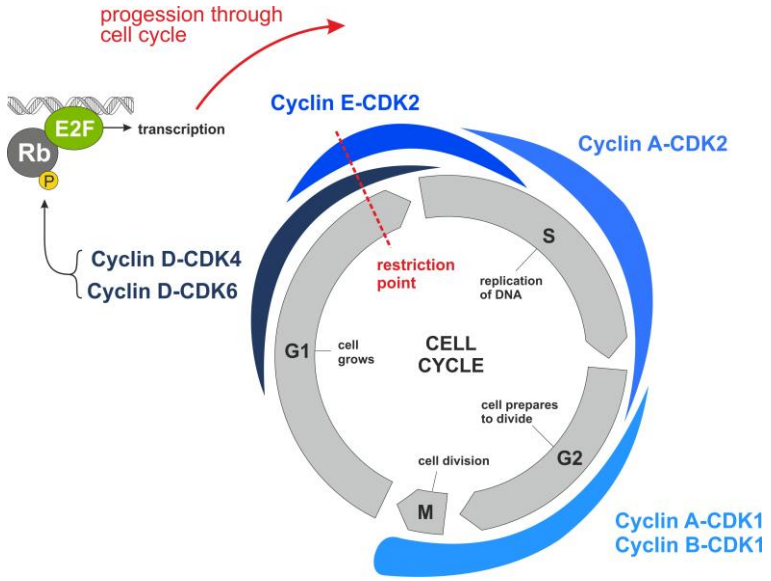
Overview

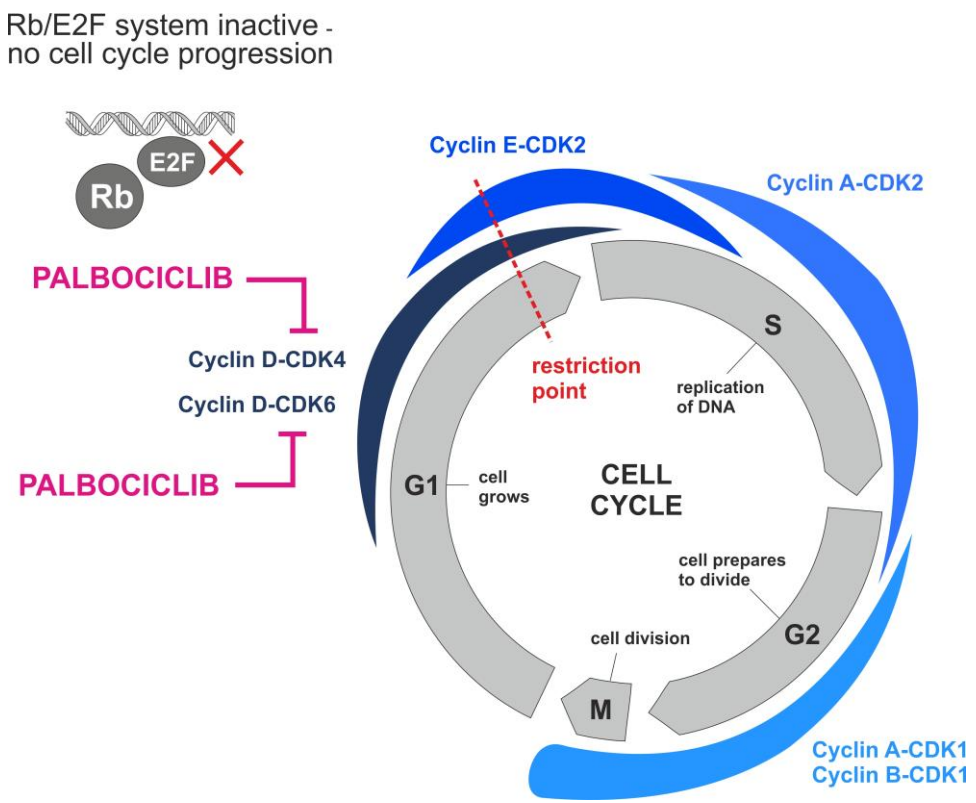
- Cyclin-dependent kinases (CDKs) play important roles in the control of cell division and modulate transcription in response to several extra- and intracellular cues
- The cyclin D–CDK4/6–retinoblastoma (Rb) pathway plays a key role in the G1 phase of the cell cycle. Phosphorylation of Rb and subsequent E2F-mediated transcription are required for G1 cell-cycle progression
- Aberrations in the cell-cycle have been implicated in human cancer pathogenesis



The Rb tumor suppressor protein plays a pivotal role in the negative control of the cell cycle. It is responsible for a major G1 checkpoint, blocking S-phase entry and cell growth. Phosphorylation leads to functional inactivation of Rb. Loss of Rb cell cycle–suppressive functions can be mediated through multiple mechanisms: loss of Rb, increased signaling through CDK4 & 6 amplification, overexpression or aberration of cyclin D/E, and loss of the inhibitory function of gene products, such as CDKN2A/B the latter leading to CDK4/6 activity.

Makumbres M. Cyclin-dependent kinases. *Genome Biol*. 2014:15:122. Helsten T et al. Cell-cycle gene alterations in 4,864 tumors analyzed by next-generation sequencing: implications for targeted therapeutics. *Mol Cancer Ther*. 2016;15:1682-1690. Pfizer, Inc. IBRANCE© (palbociclib) US Prescribing Information. Helsten T et al. Cell-cycle gene alterations in 4,864 tumors analyzed by next-generation sequencing: implications for targeted therapeutics. *Mol Cancer Ther*. 2016;15:1682-1690.

Mechanism of Action



- Palbociclib is an inhibitor of CDKs 4 and 6, and blocked cell cycle progression of estrogen receptor (ER)-positive breast cancer cell lines from G1 to S *in vitro*.
- *In vivo*, the combination of palbociclib and letrozole inhibited Rb phosphorylation, downstream signaling, and tumor growth compared to each drug alone using a patient-derived ER-positive breast cancer xenograft model

Helsten T et al. Cell-cycle gene alterations in 4,864 tumors analyzed by next-generation sequencing: implications for targeted therapeutics. *Mol Cancer Ther*. 2016;15:1682-1690.

Stage of Development

Palbociclib is being investigated in combination with other agent(s) in the tumor types shown here. Palbociclib is not approved for the uses listed below.

HR+/HER2- Adjuvant Breast Cancer	Phase 3: Combination*
HR+/HER2+ Metastatic Breast Cancer	Phase 3: Combination◊
Pediatric Patients with Advanced Solid Tumors	Phase 1: Combination

*Sponsored by German Breast Group. For high risk breast cancer patients. Closed to enrollment.
◊Sponsored by Alliance Foundation Trials, LLC.

ClinicalTrials.gov. Accessed August 3, 2020. http://clinicaltrials.gov/

Development Program

August 2020

Talazoparib

PARP Inhibitor

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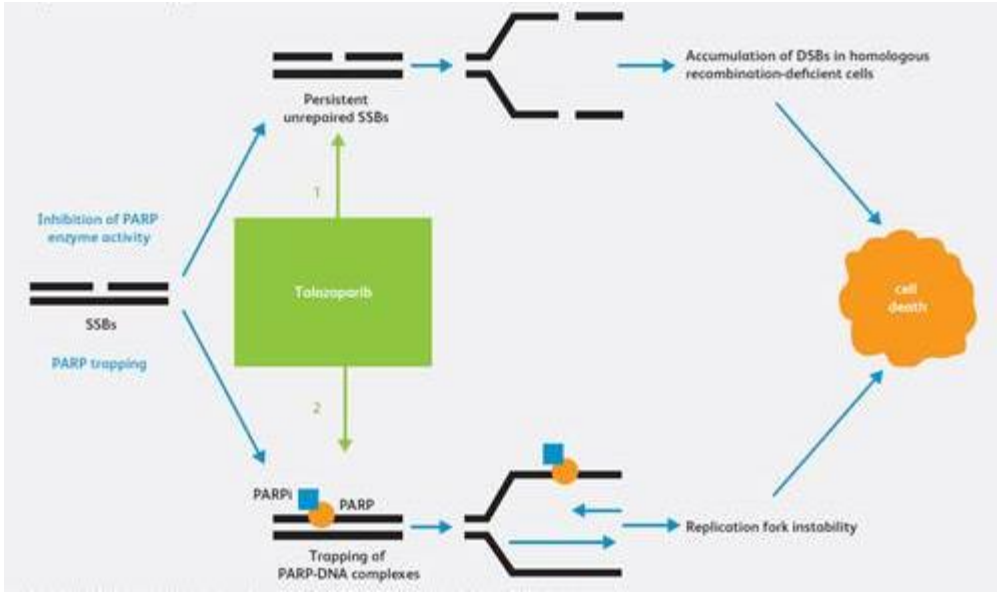
Overview

- DNA double-strand breaks (DSBs) frequently arise in cells and, if left unrepaired, cause senescence or cell death. Homologous recombination (HR) and nonhomologous end-joining (NHEJ) are the 2 major DSB DNA-repair pathways
- BRCA1 and BRCA2 are key DNA-Damage Repair (DDR) proteins in the homologous recombination pathway
- Cells with defective BRCA have compromised ability to repair DSBs
- Poly (ADP-ribose) polymerase (PARP) is an enzyme associated with single-strand, base-excision repair and can enable DNA replication and cell survival in BRCA-deficient tumor cells
- By inhibiting PARP in cells with defective BRCA, the cells are unable to repair accumulated DNA damage and undergo cell death (synthetic lethality)
- Talazoparib is a dual inhibitor of nuclear PARP enzymes with antineoplastic activity
- Talazoparib is designed to inhibit the PARP enzyme and trap PARP on DNA
- Talazoparib selectively binds to PARP and prevents PARP-mediated DNA repair of single-strand DNA breaks via the base-excision repair pathway
  - This enhances the accumulation of DNA strand breaks, promotes genomic instability and eventually leads to apoptosis
- Preventing PARP-mediated DNA damage repair thereby induces tumor cell death in BRCA1/2-mutated tumor cells

Her J, Bunting SF. How cells ensure correct repair of DNA double-strand breaks. *J Biol Chem*. 2018;293:10502-10511. Chappell WH et al. Homologous recombination repair factors Rad51 and BRCA1 are necessary for productive replication of human papillomavirus 31. *J Virol*. 2015;90:2639-2652. Talazoparib. Published 2017. Accessed February 23, 2020. https://pfe-pfizercom-prod.s3.amazonaws.com/news/asco/Talazoparib_Fact_Sheet.pdf. Wang Y et al. Computational investigation of homologous recombination DNA repair deficiency in sporadic breast cancer. *Sci Rep*. 2017;16:15742. National Cancer Institute. NCI Drug Dictionary: talazoparib tosylate. Accessed February 23, 2020. https://www.cancer.gov/publications/dictionaries/cancer-drug/def/talazoparib. Pfizer, Inc. TALZENNA™ (talazoparib) US Prescribing Information.

Mechanism of Action



Possible dual cytotoxic mechanisms of PARP inhibitors:

1. Catalytic inhibition of PARP is thought to interfere with the repair of DNA single-strand breaks (SSBs).
2. Talazoparib is believed to trap the PARP on SSBs, based on preclinical data, preventing dissociation from damaged DNA, leading to replication fork instability.

Murai J et al. Trapping of PARP1 and PARP2 by clinical PARP inhibitors. *Cancer Res*. 2012;72:5588-5599. Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. *Science. 2017;*355:1152-1158.

Figure from Agarwal N et al.,TALAPRO-2: A Placebo-controlled Phase 3 Study of Talazoparib Plus Enzalutamide for Patients With First-line Metastatic Castration-resistant Prostate Cancer presented at the ASCO-GU 2020 Annual Meeting • February 13-15, 2020.

Stage of Development

Talazoparib is being investigated as a single agent or in combination with other agent(s) in the tumor types shown here. Talazoparib is not approved for the uses listed below.

Metastatic Castration-Resistant Prostate Cancer (mCRPC)	Phase 3 Combination Phase 2*
Neoadjuvant Early TNBC with Germline BRCA Mutations	Phase 2*
BRCA or ATM Mutant Solid Tumors	Phase 2 Combination *
RAS Mutant Solid Tumors	Phase 2 Combination

*Closed to enrollment.

ClinicalTrials.gov. Accessed August 3, 2020. http://clinicaltrials.gov/