Notice

- The preclinical data included in this presentation are not intended to imply clinical benefit
- The efficacy and safety of the investigational compounds discussed in this deck have not been established
- There is no guarantee that these compounds will become commercially available for the use(s) under investigation

AACR American Association for Cancer Research
ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

Development of a CDK2-Selective Small Molecule Inhibitor INCB123667 for the Treatment of *CCNE1*^{high} Breast Cancers

Saswati Chand, Michael Hansbury, Yvonne Lo, Michelle Kinder, Kathy Wang, Qian Wang Yao, Derek Zimmer, Katherine Drake, Pat Feldman, Justine Carl, Cynthia Timmers, Joshua Hummel, Susan Wee, Sunkyu Kim

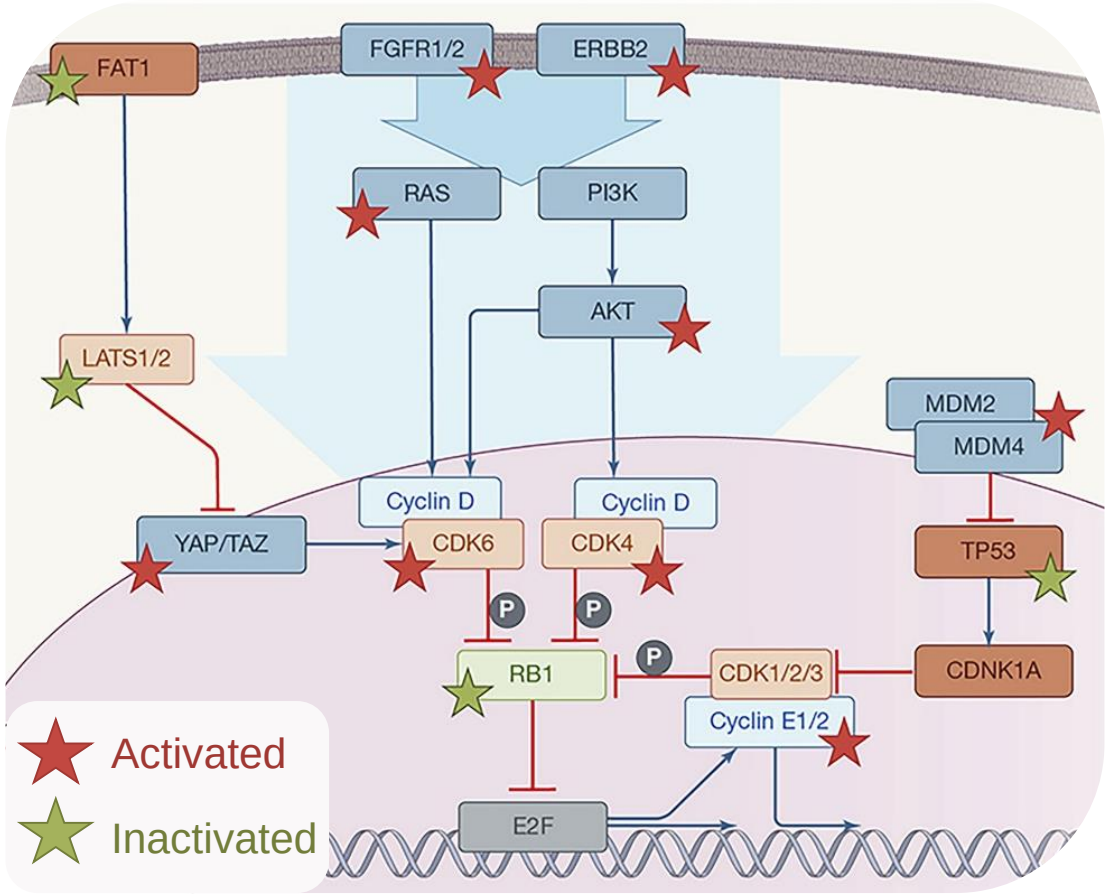
Incyte Research Institute, Wilmington, DE

Abstract 1143

Development of Resistance to CDK4/6 Inhibitors Is Common in Advanced Breast Cancer

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

- Primary resistance: About 15% of patients treated with CDK4/6 inhibitor (CDK4/6i) + aromatase inhibitor, and up to 30% of those treated with CDK4/6i + fulvestrant, will develop recurrent disease within 6 months
- Acquired resistance: Almost all patients will eventually develop progressive disease
- Multiple pathways are implicated in resistance
- *CCNE1* amplification and cyclin E1 overexpression are
  - Predictive for resistance to CDK4/6i
  - Associated with poor clinical outcomes



Reprinted from Álvarez-Fernández M, Malumbres M. *Cancer Cell*. 2020;37:514-529. Copyright © 2020 with permission from Elsevier Inc.

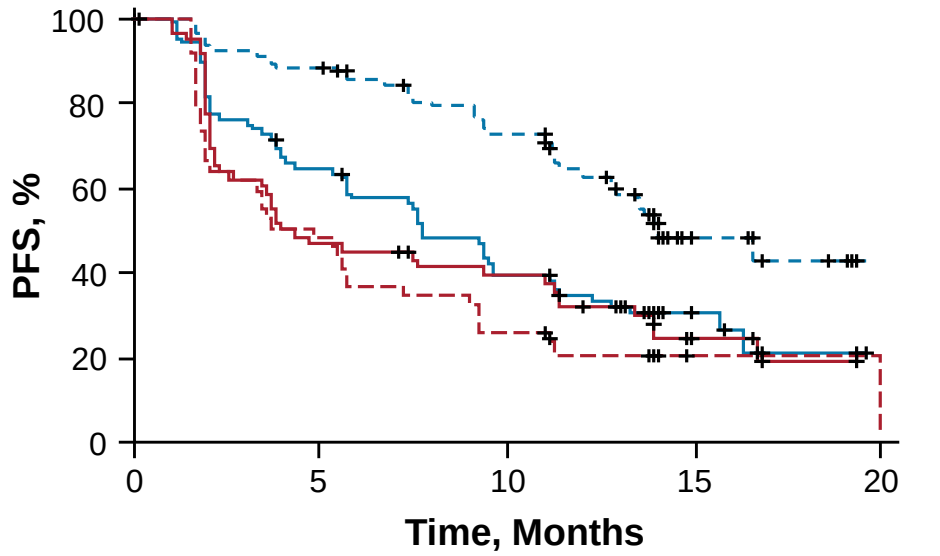
Álvarez-Fernández M, Malumbres M. *Cancer Cell*. 2020;37:514-529. Migliaccio I, et al. *Cancer Treat Rev*. 2021;93:102136. Turner NC, et al. *J Clin Oncol*. 2019;37:1169-1178. Chan AM, et al. *J Pathol Clin Res.* 2020;6:252-262.

High *CCNE1* Expression Is Predictive for Resistance to CDK4/6i in HR^{+}HER2^{-} Breast Cancer

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

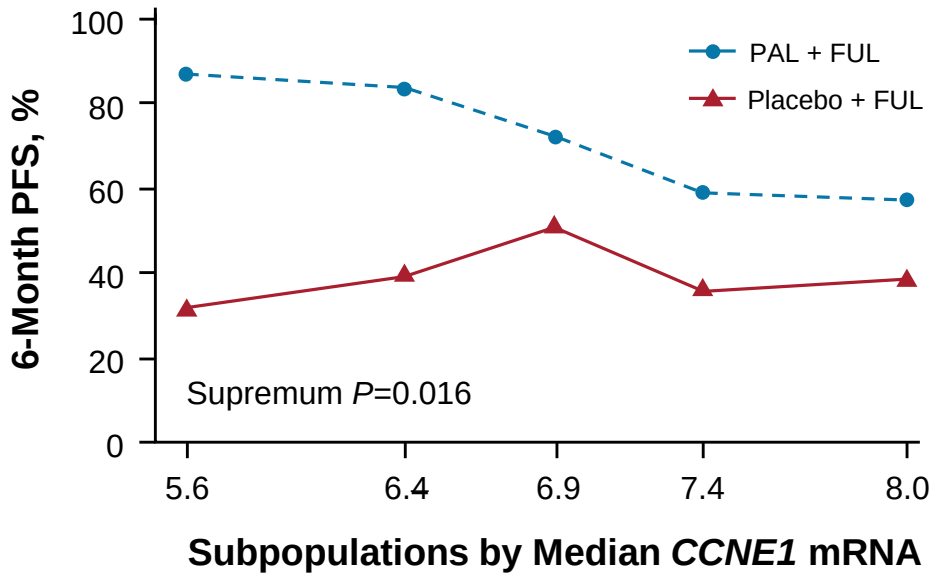
High *CCNE1* mRNA expression is associated with primary resistance to CDK4/6i palbociclib (PALOMA-3 trial)

A



Low *CCNE1* expression, PAL + FUL (n=103; mPFS=14.1 months)
Low *CCNE1* expression, placebo + FUL (n=48; mPFS=4.8 months)
High *CCNE1* expression, PAL + FUL (n=91; mPFS=7.6 months)
High *CCNE1* expression, placebo + FUL (n=60; mPFS=4.0 months)

B



CDK4/6i, CDK4/6 inhibitor; FUL, fulvestrant; mPFS, median progression-free survival; PFS, progression-free survival; PAL, palbociclib.

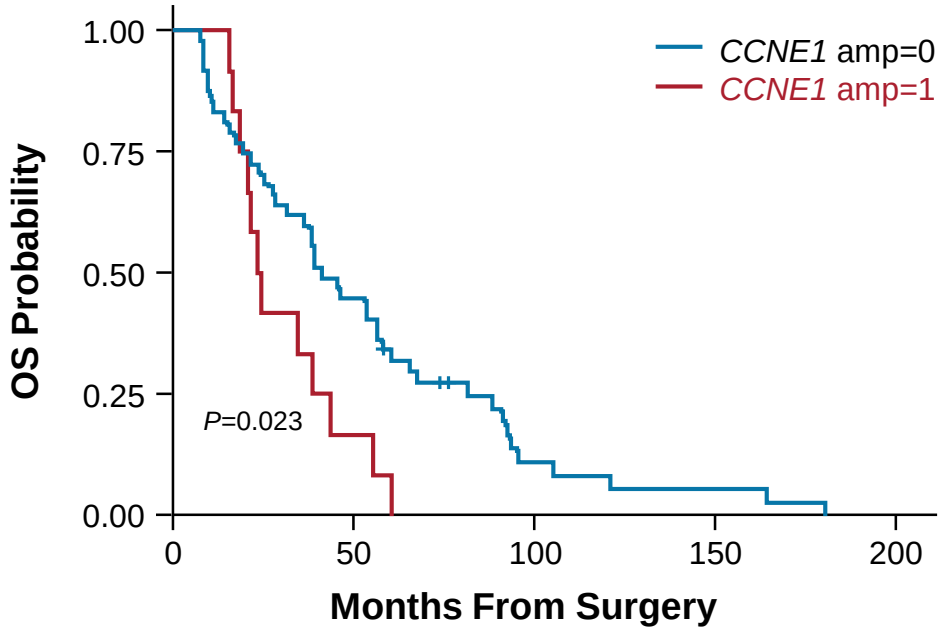
Turner NC, et al. *J Clin Oncol*. 2019;37:1169-1178.

CCNE1 Amplification Is Associated With Poor Prognosis in Patients With TNBC

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

TNBCs with *CCNE1* amplification (copy number >6) correlate with poor OS

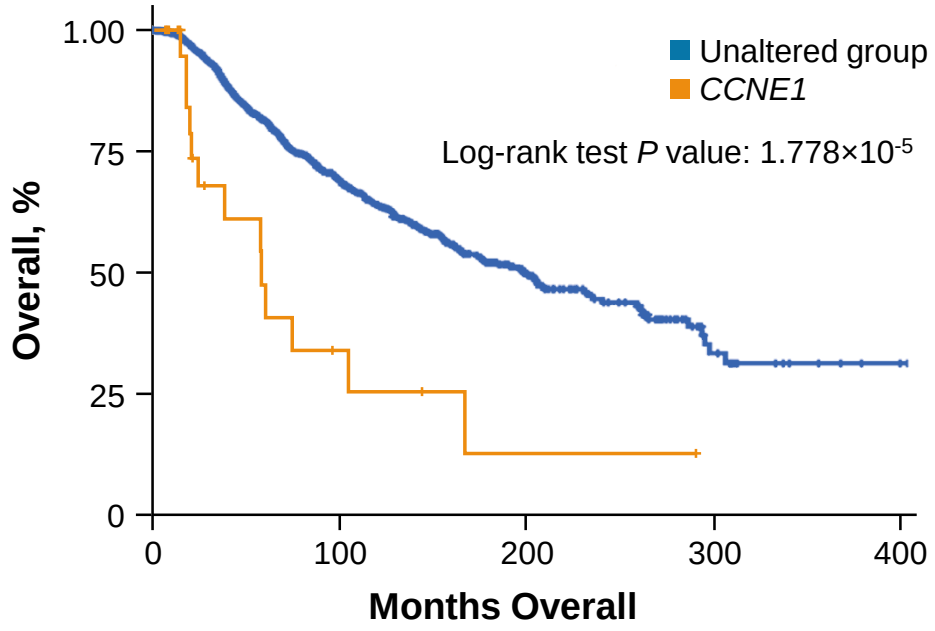
A



CCNE1 Amp	TCGA	METABRIC
TNBC	9.48%	5.66%

TNBCs with high *CCNE1* expression correlate with poor OS (cBioPortal)

B



METABRIC, Molecular Taxonomy of Breast Cancer International Symposium; OS, overall survival; TCGA, The Cancer Genome Atlas; TNBC, triple-negative breast cancer.

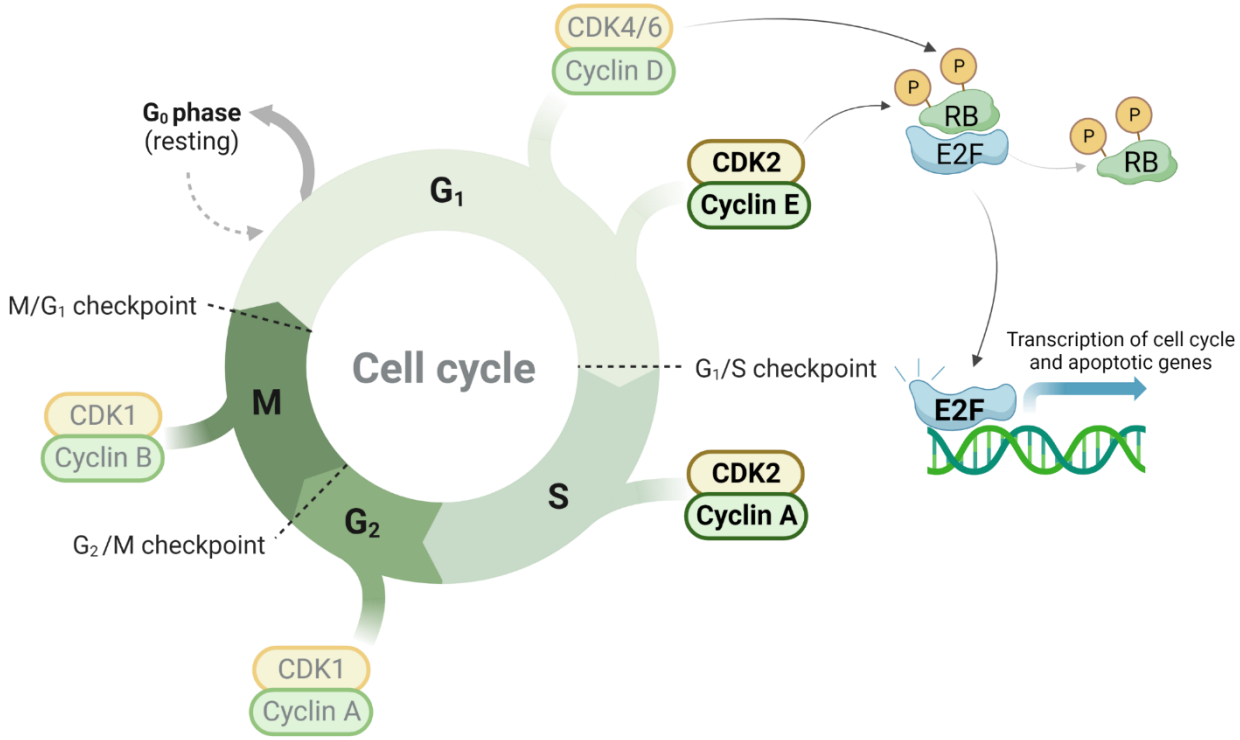
Zhao Z-M, et al. *BMC Cancer*. 2019;19:96. TCGA. Available from: https://portal.gdc.cancer.gov/ (accessed on 11/18/22). Yuan Q, et al. *World J Surg Oncol*. 2021;19:86.

CCNE1 Amplification Has Synthetic Lethality With CDK2 Inhibition

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

- *CCNE1* amplification and cyclin E overexpression in cancer cells are predictive of CDK2 dependency as demonstrated by genetic knockdown studies
- CDK2 in complex with cyclin E regulates the G1/S transition and promotes DNA replication during the cell cycle
- Patients with primary or acquired *CCNE1* amplification and cyclin E overexpression may benefit from CDK2-targeted therapy

Role of CDK2/CCNE1 Complex in the Cell Cycle



Used with permission of EUREKA SCIENCE (FZC) from Treating Neurodegenerative Conditions Through the Understanding of Neuronal Apoptosis. D'Mello SR, et al. *Curr Drug Targets - CNS Neurol Disord*. 2005;4(1); permission conveyed through Copyright Clearance Center, Inc.
RB, retinoblastoma protein.

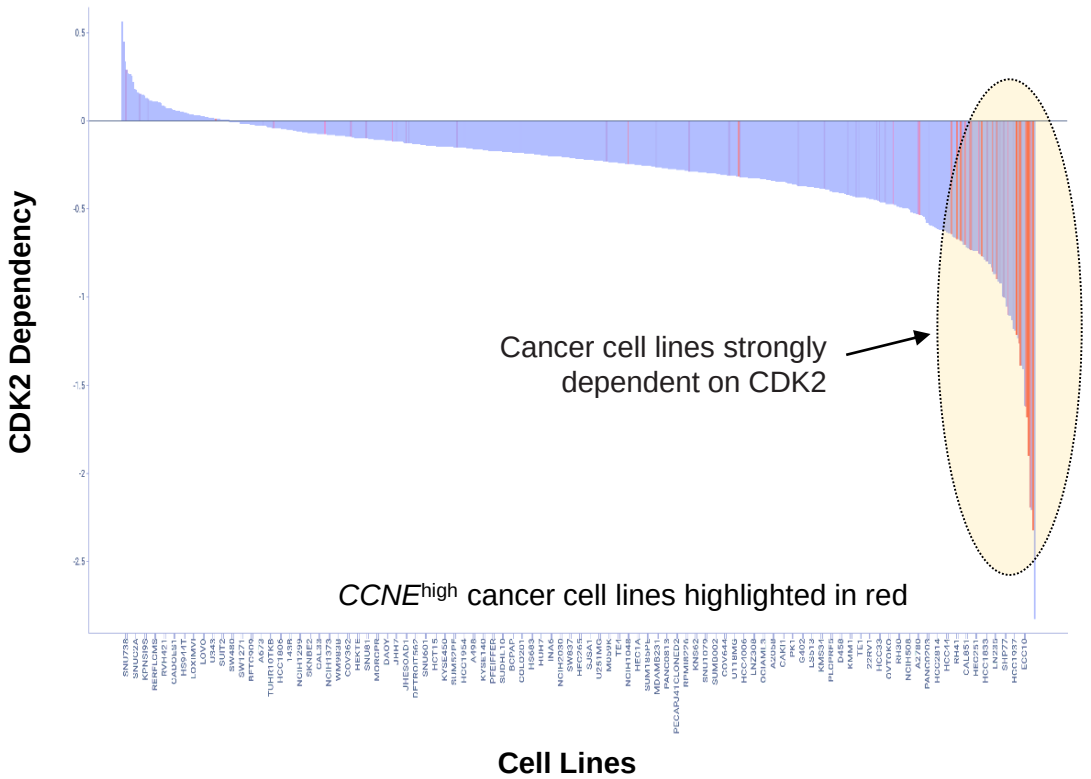
Etemadmoghadam D, et al. *Clin Cancer Res*. 2013;19:5960-5971.

CCNE1-Amplified or Overexpressed Cancer Cells Are Dependent on CDK2

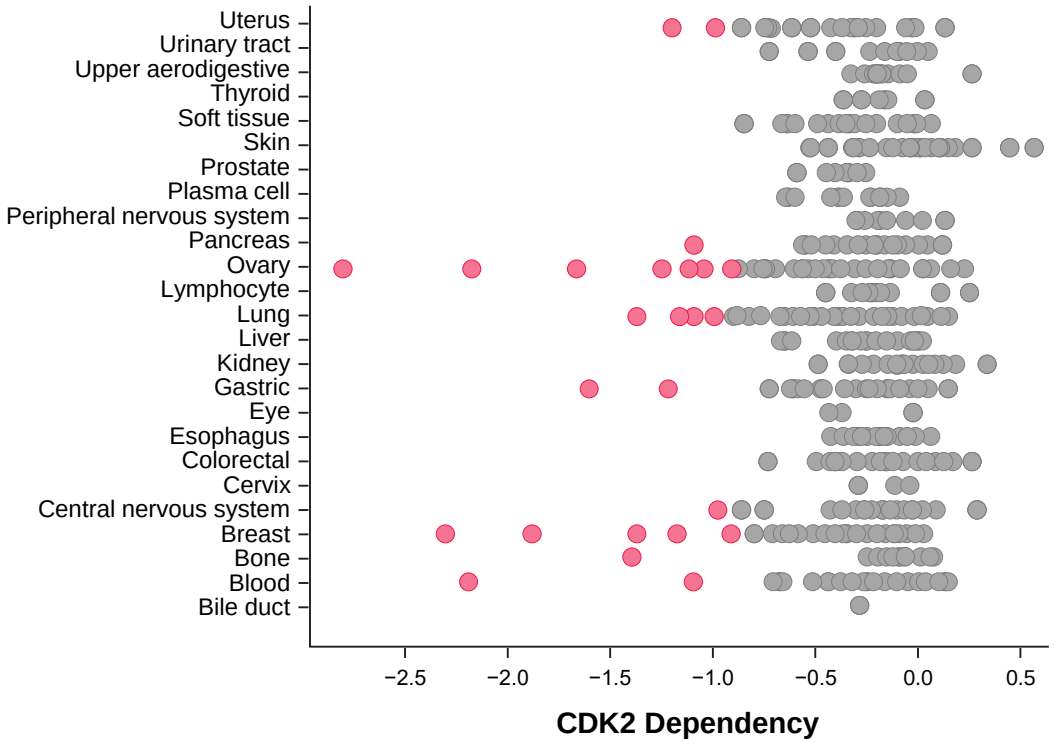
AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

Project Achilles data from the DepMap portal indicate most CDK2-dependent cancer cell lines harbor *CCNE1* amplification or overexpression across multiple lineages

A



B



Modified from Wee S, et al. *Eur J Cancer.* 2022;174:S79. DepMap, Dependency Map.

Biochemical and Cellular Assays Demonstrate INCB123667 Is a Potent and Selective CDK2 Inhibitor

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

CDK Target	Biochemical Assay IC_{50}, μM	Cellular Assay IC_{50}, μM
CDK2	0.00087	0.053
CDK1	0.195	0.692
CDK4	0.046	0.873
CDK6	0.206	1.582
CDK7	0.355	>10,000
CDK9	3.676	5.273

IC_{50}, half-maximal inhibitory concentration.

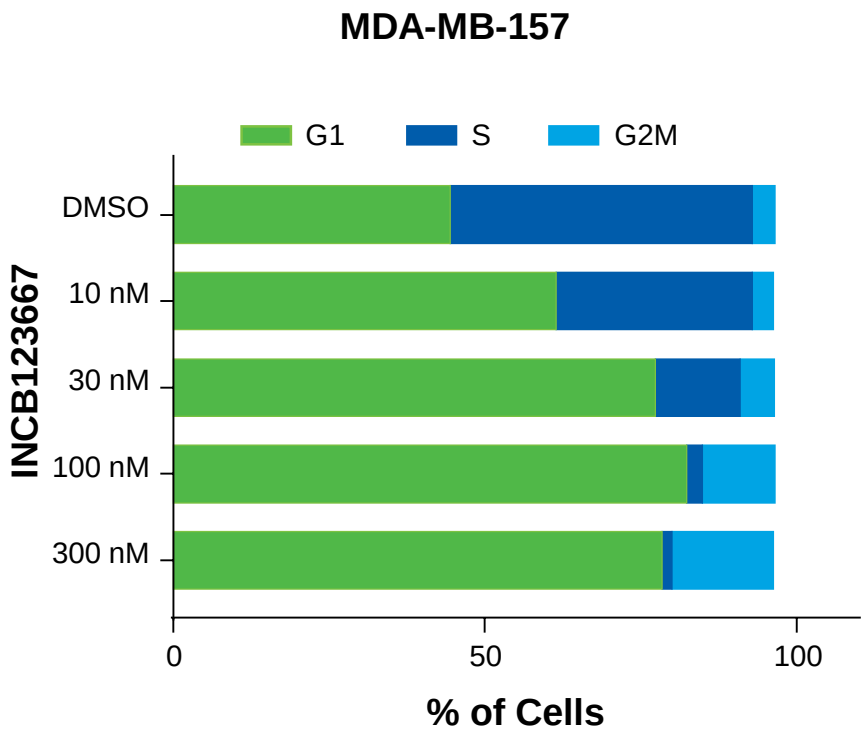
Wee S, et al. *Eur J Cancer.* 2022;174:S79.

INCB123667 Blocks G1/S Transition and Induces Senescence in *CCNE1*^{high} Breast Cancer Cells

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

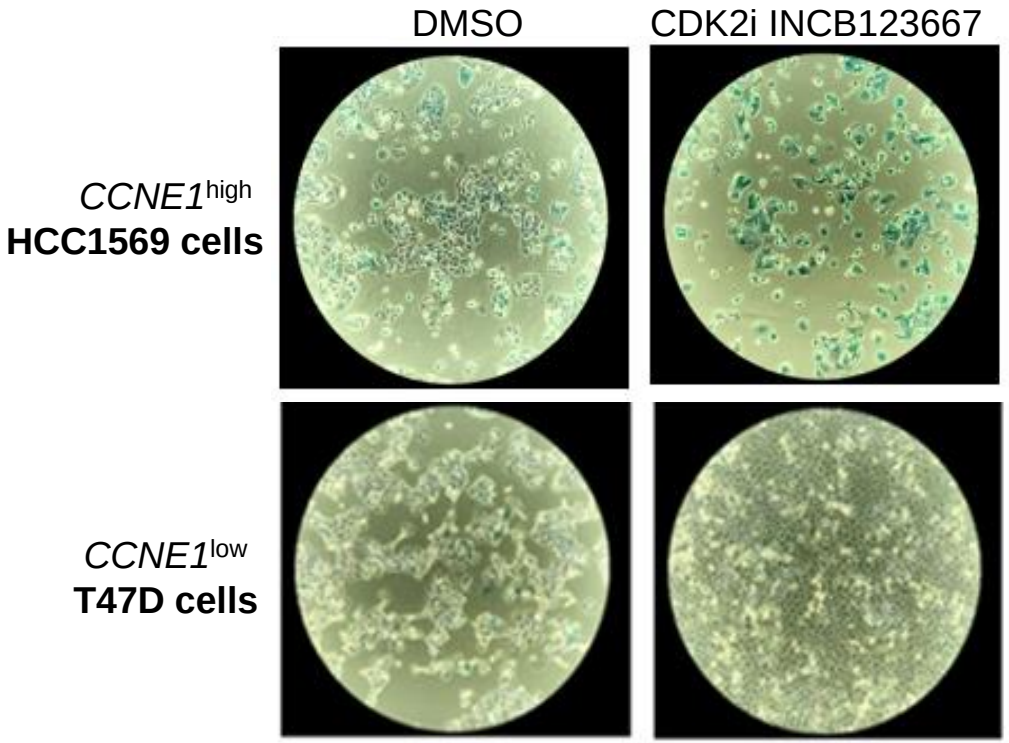
INCB123667 blocks G1/S transition in *CCNE1*^{high} cells

A



INCB123667 induces senescence in *CCNE1*^{high} cells

B



Senescence demonstrated by beta-galactosidase (SA-βgal) staining

DMSO, dimethyl sulfoxide.

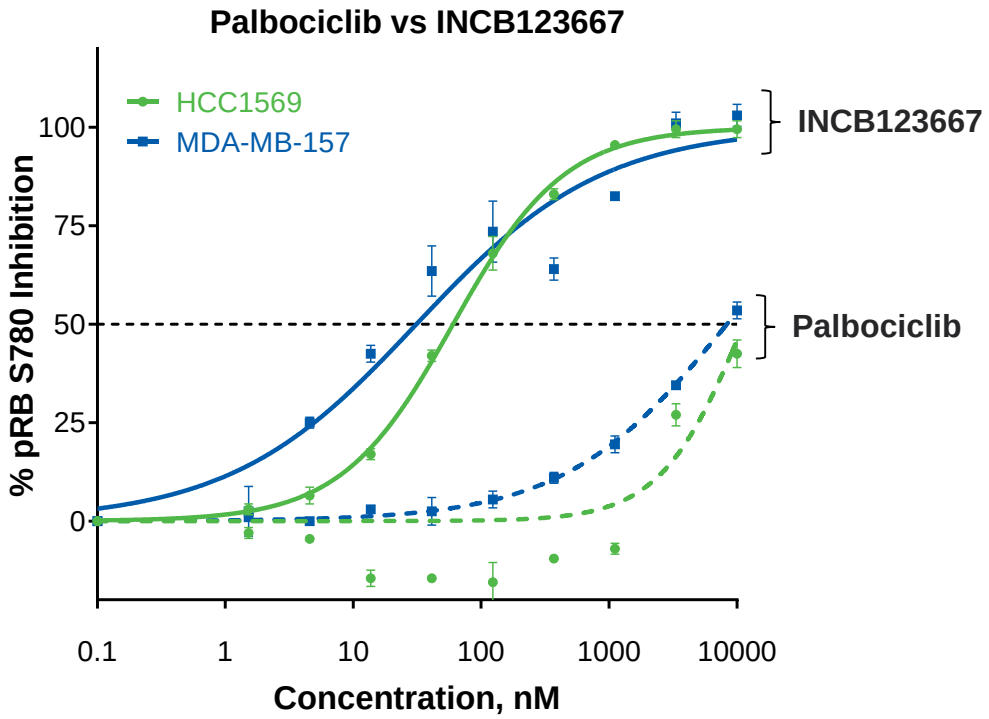
Wee S, et al. *Eur J Cancer.* 2022;174:S79.

INCB123667 Induces Potent pRB and Growth Inhibition in Palbociclib-Resistant *CCNE1*^{high} Breast Cancer Cell Lines

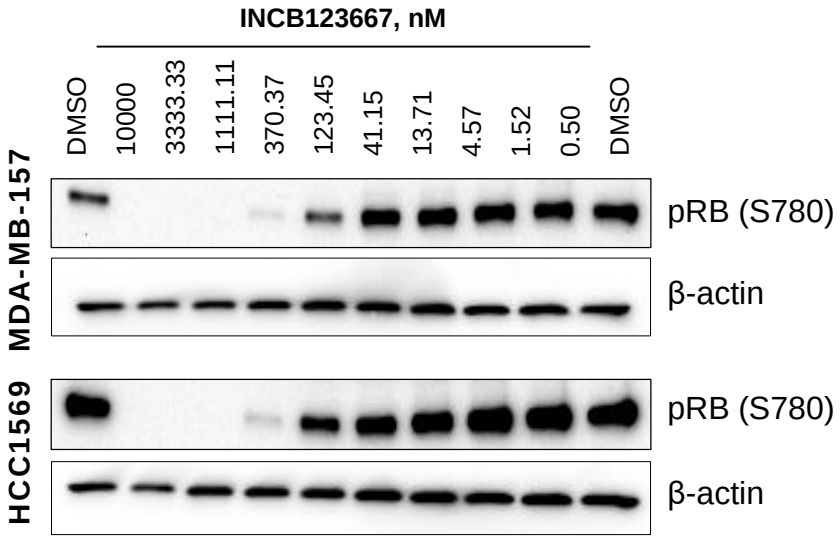
AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

INCB123667 inhibits pRB in *CCNE1*^{high} breast cancer cells in vitro

A



B

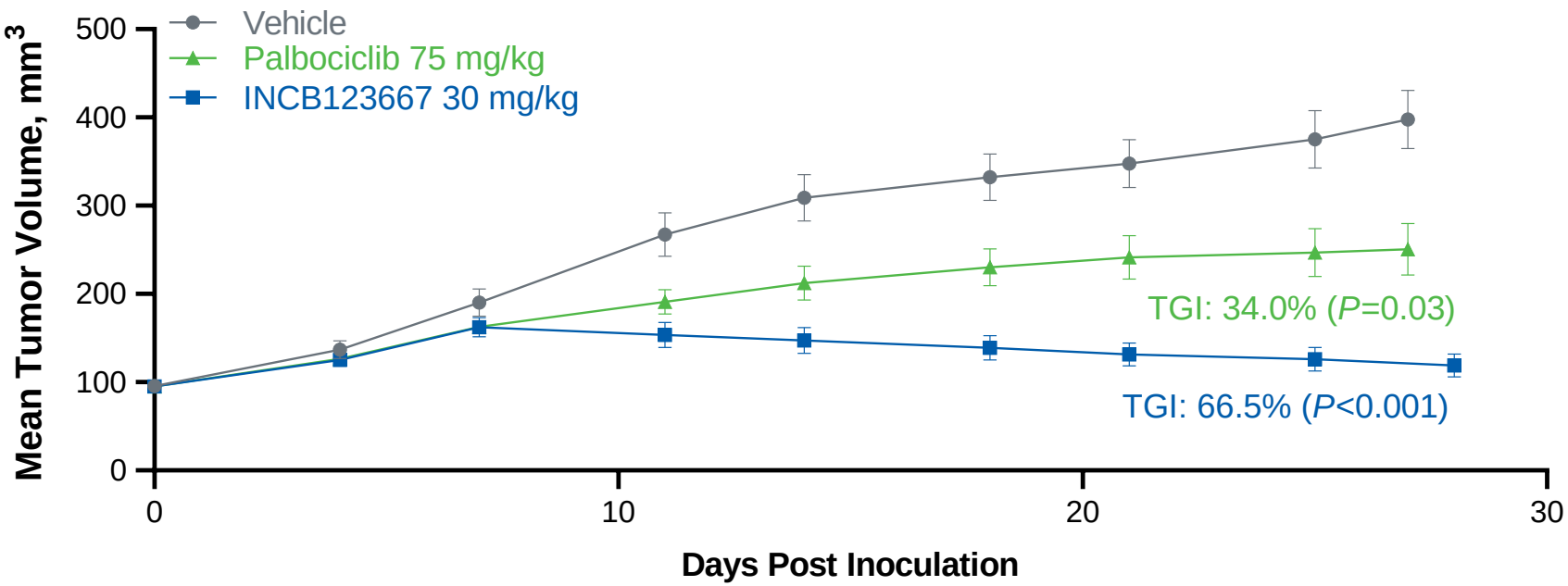


DMSO, dimethyl sulfoxide; pRB, phosphorylated retinoblastoma protein.

INCB123667 Inhibited Tumor Growth in *CCNE1*^{high} HCC1569 Xenograft Model In Vivo

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

INCB123667 inhibited tumor growth by 66.5% (*P*<0.001) vs a tumor growth inhibition (TGI) of 34% by palbociclib in an HR$^-$/HER2$^+$ epithelial breast cancer line HCC1569 xenograft model in NSG/SCID mice

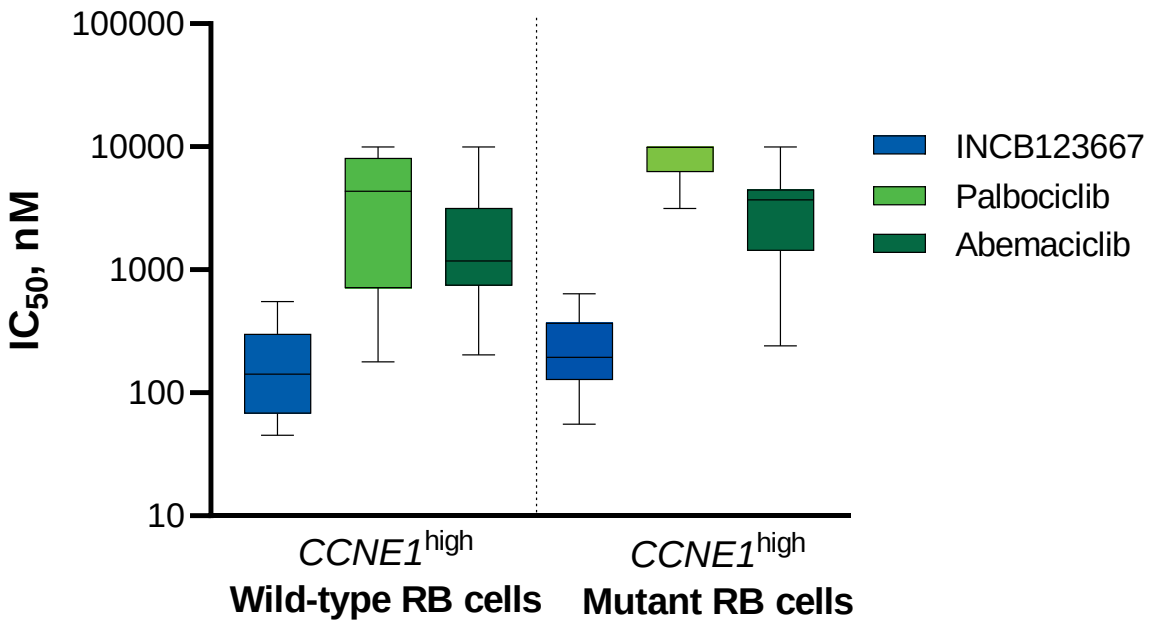


RB1 Loss Is Both an Intrinsic and Acquired Mechanism of Resistance to CDK4/6 Inhibition

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

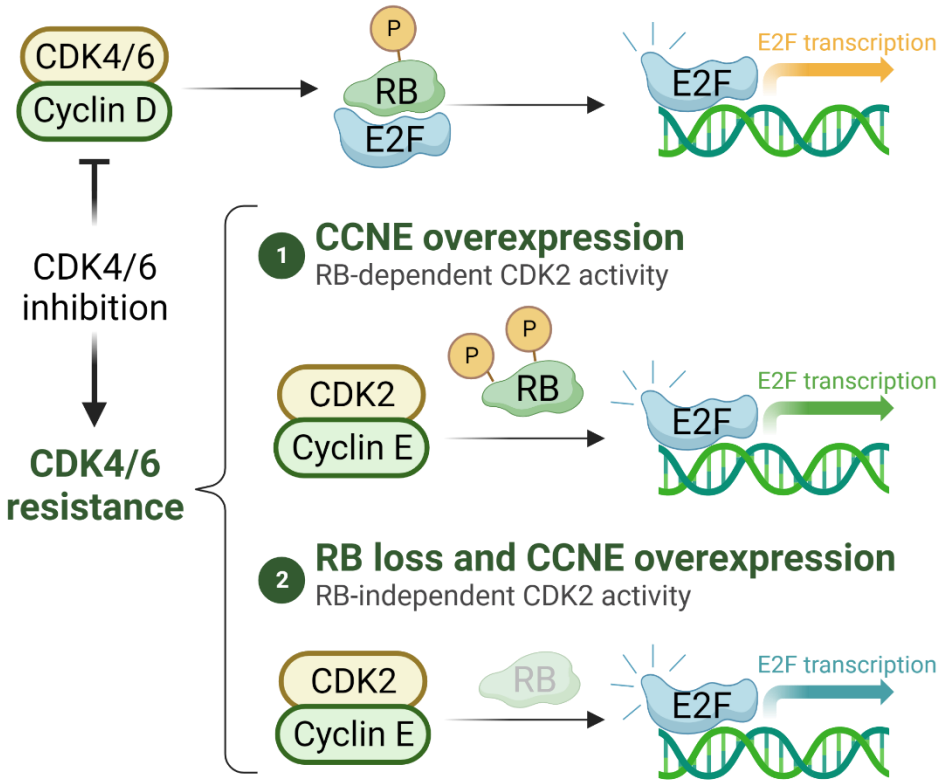
INCB123667 inhibits RB wild-type and RB-mutant *CCNE1*^{high} cell growth in vitro

A



Cyclin E1/CDK2 remains active in RB-mutant *CCNE1*^{high} tumor cells

B



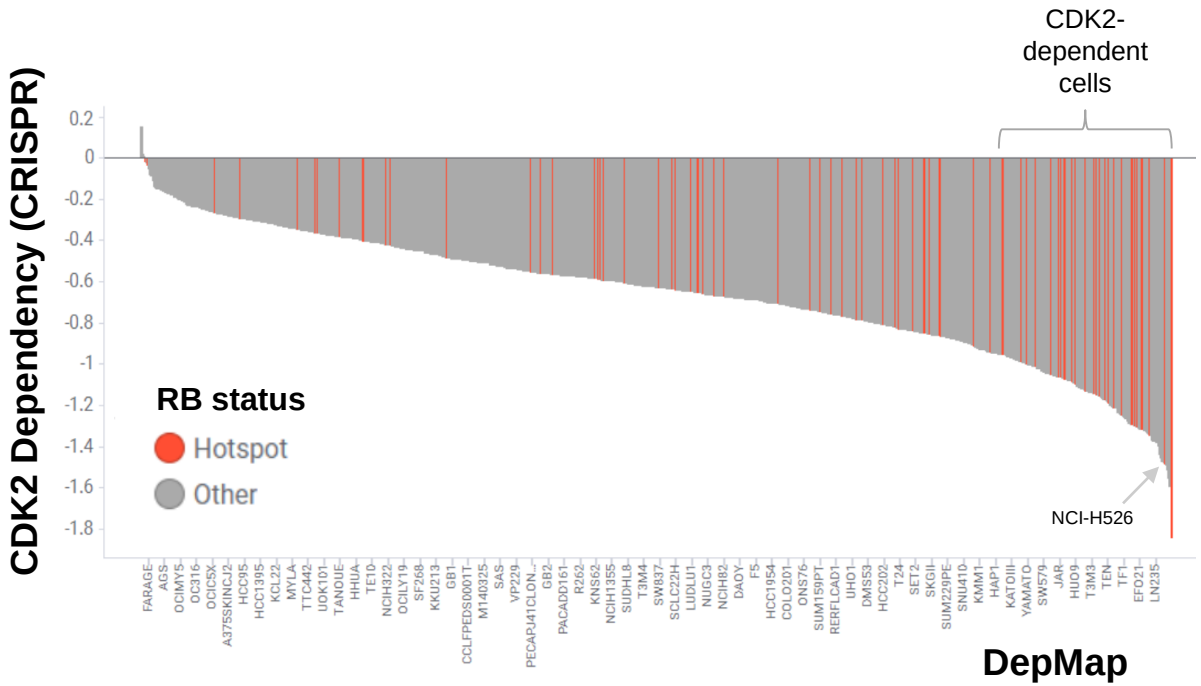
IC_{50}, half-maximal inhibitory concentration; RB, retinoblastoma protein.

INCB123667 Is Active in RB Wild-Type and RB-Mutant Cells

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

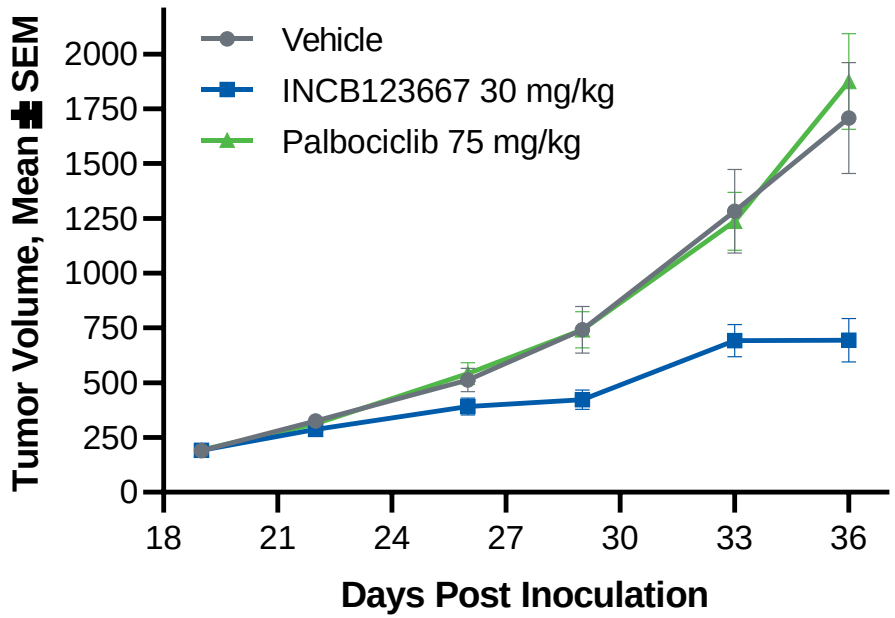
CCNE1^{high} RB-mutant cancer lines are dependent on CDK2 in pan-cancer analysis

A



INCB123667 inhibits tumor growth in NCI-H526 RB-mutant in vivo tumor model

B



RB, retinoblastoma protein; SEM, standard error of the mean.
Source: Broad Institute. DepMap. https://depmap.org/portal/.

First-in-Human Phase 1b Trial of INCB123667 in Selected *CCNE1*^{high} Patients With Advanced Malignancies

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

Phase 1a – Dose Escalation

Monotherapy
INCB123667

Identification of RDE(s)

Phase 1b – Dose Expansion
***CCNE1*^{high} Tumors**

- Triple-negative breast cancer
- HR^{+}HER2^{-} BC after progression or intolerance of CDK4/6i treatment*
- Ovarian/fallopian/primary peritoneal cancer
- Endometrial/uterine cancer
- GI malignancies
- Other tumor-agnostic indications

*No selection for *CCNE1*^{high}.
BC, breast cancer; CDK4/6i, CDK4/6 inhibitor; GI, gastrointestinal; RDE, recommended dose for expansion.
ClinicalTrials.gov Identifier: NCT05238922.

Authors' Summary

- INCB123667 is a selective and potent CDK2 kinase inhibitor with subnanomolar inhibitory activity against human CDK2/cyclin E1
- INCB123667 selectively inhibited RB phosphorylation, blocked G1-S transition, and induced cell growth inhibition in *CCNE1*^{high} preclinical breast cancer cell lines in vitro
- INCB123667 exhibited significant single-agent activity in vivo in *CCNE1*^{high} breast cancer xenograft
- INCB123667 inhibited RB-mutant and RB wild-type *CCNE1*^{high} cancer cells in vitro and in vivo
- A phase 1 clinical trial of INCB123667 in patients with advanced malignancies including *CCNE1*^{high} TNBC and HR^{+}HER2^{-} tumors post-CDK4/6i is ongoing (NCT05238922)

CDK4/6i, CDK4/6 inhibitor; RB, retinoblastoma protein; TNBC, triple-negative breast cancer.