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

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Abstract 1143

Disclosure Information

Saswati Chand

I have the following relevant financial relationships to disclose:

Employee of: Incyte Corporation

Stockholder in: Incyte Corporation

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

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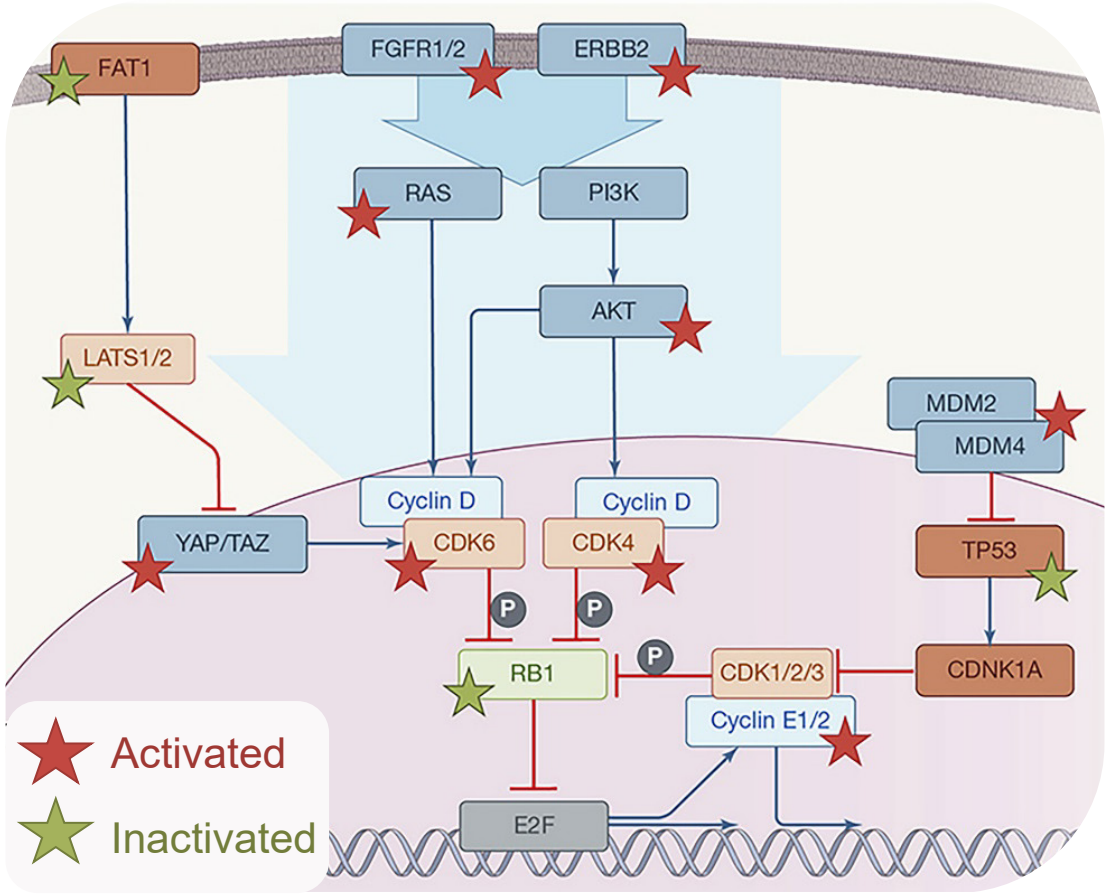
- Primary resistance: About 15% of patients treated with CDK4/6 inhibitor (CDK4/6i) + aromatase inhibitor, and up to 30% of those treated with CDK4/6i + fulvestrant, will develop recurrent disease within 6 months
- Acquired resistance: Almost all patients will eventually develop progressive disease
-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



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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

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

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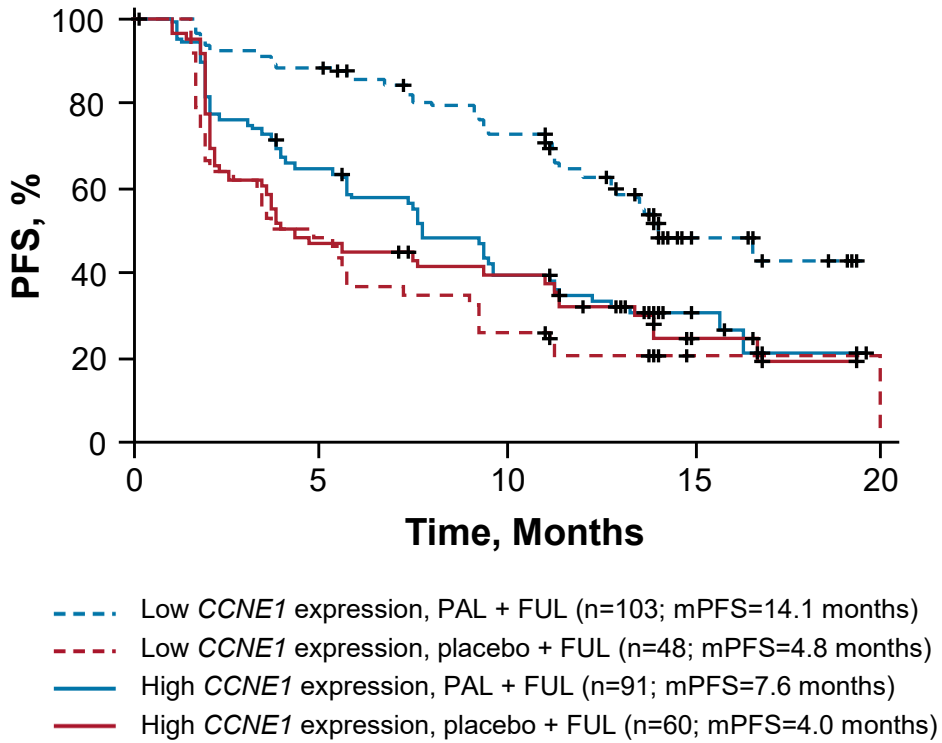

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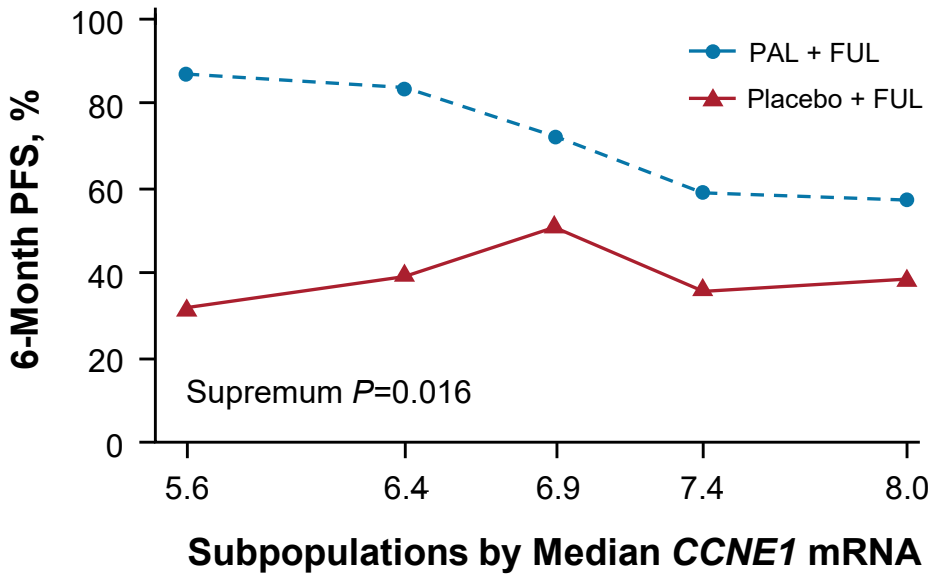

CDK4/6i, CDK4/6 inhibitor; FUL, fulvestrant; mPFS, median progression-free survival; PFS, progression-free survival; PAL, palbociclib.

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

CCNE1 Amplification Is Associated With Poor Prognosis in Patients With TNBC

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

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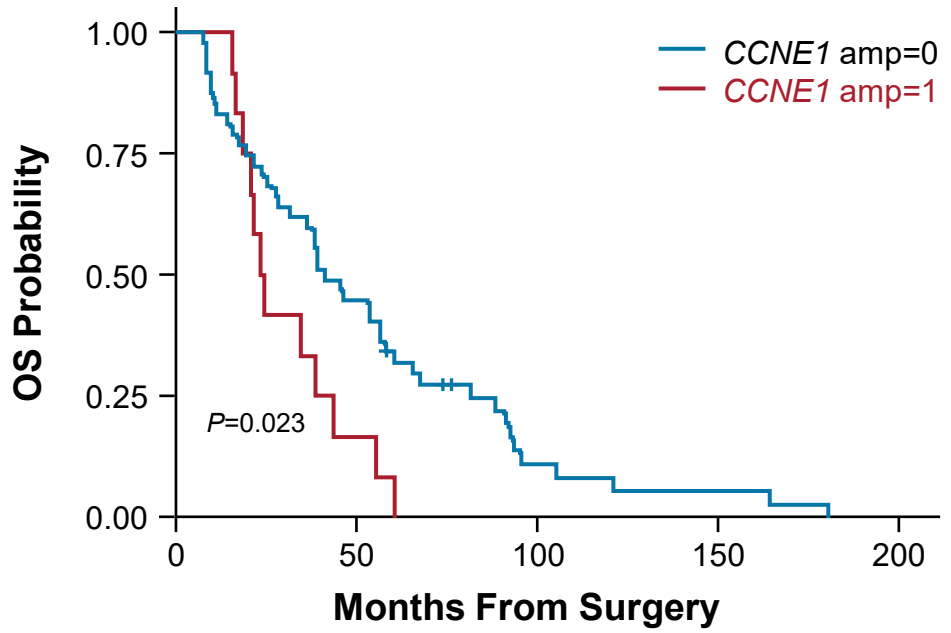

CCNE1 Amp	TCGA	METABRIC
TNBC	9.48%	5.66%

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

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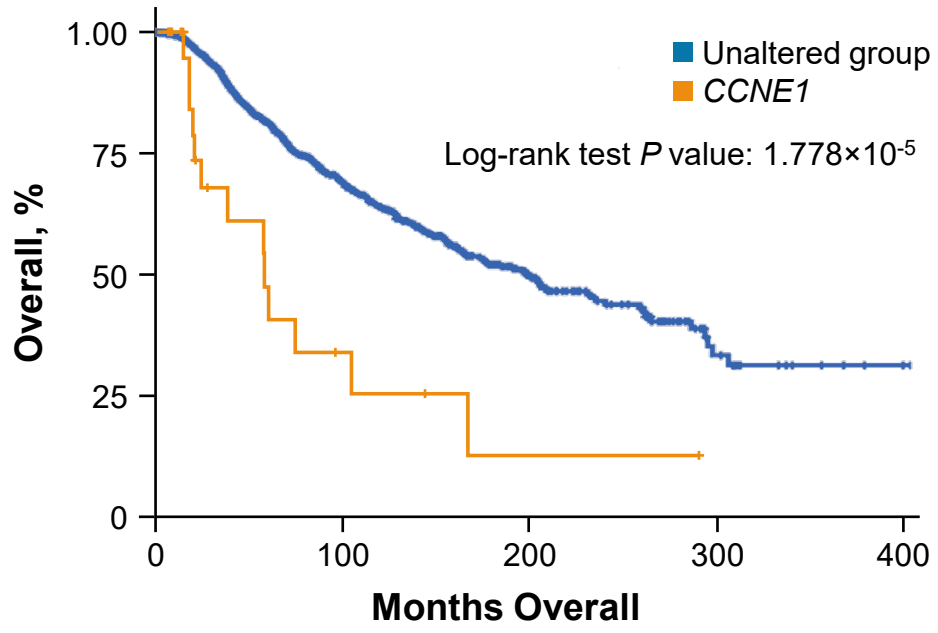

METABRIC, Molecular Taxonomy of Breast Cancer International Symposium; OS, overall survival; TCGA, The Cancer Genome Atlas; TNBC, triple-negative breast cancer.

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

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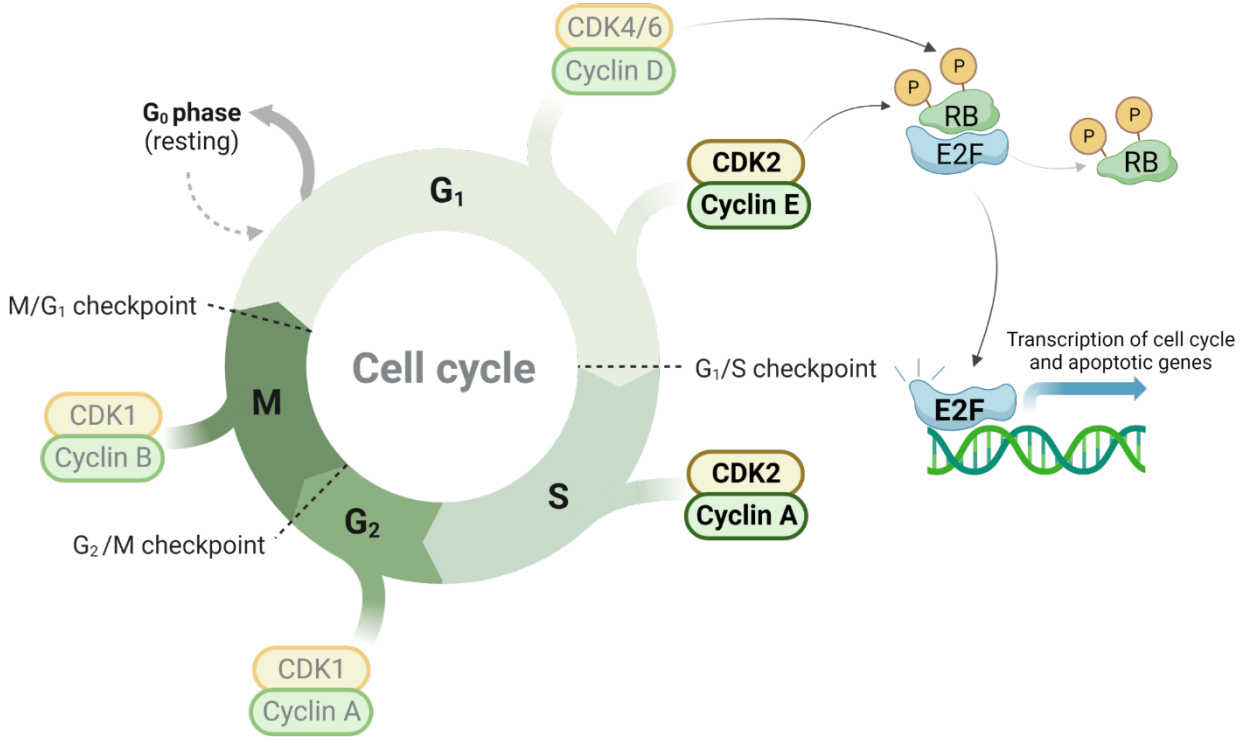
- *CCNE1* amplification and cyclin E overexpression in cancer cells are predictive of CDK2 dependency as demonstrated by genetic knockdown studies
- CDK2 in complex with cyclin E regulates the G1/S transition and promotes DNA replication during the cell cycle
- Patients with primary or acquired *CCNE1*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

Role of CDK2/CCNE1 Complex in the Cell Cycle



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RB, retinoblastoma protein.

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

CCNE1-Amplified or Overexpressed Cancer Cells Are Dependent on CDK2

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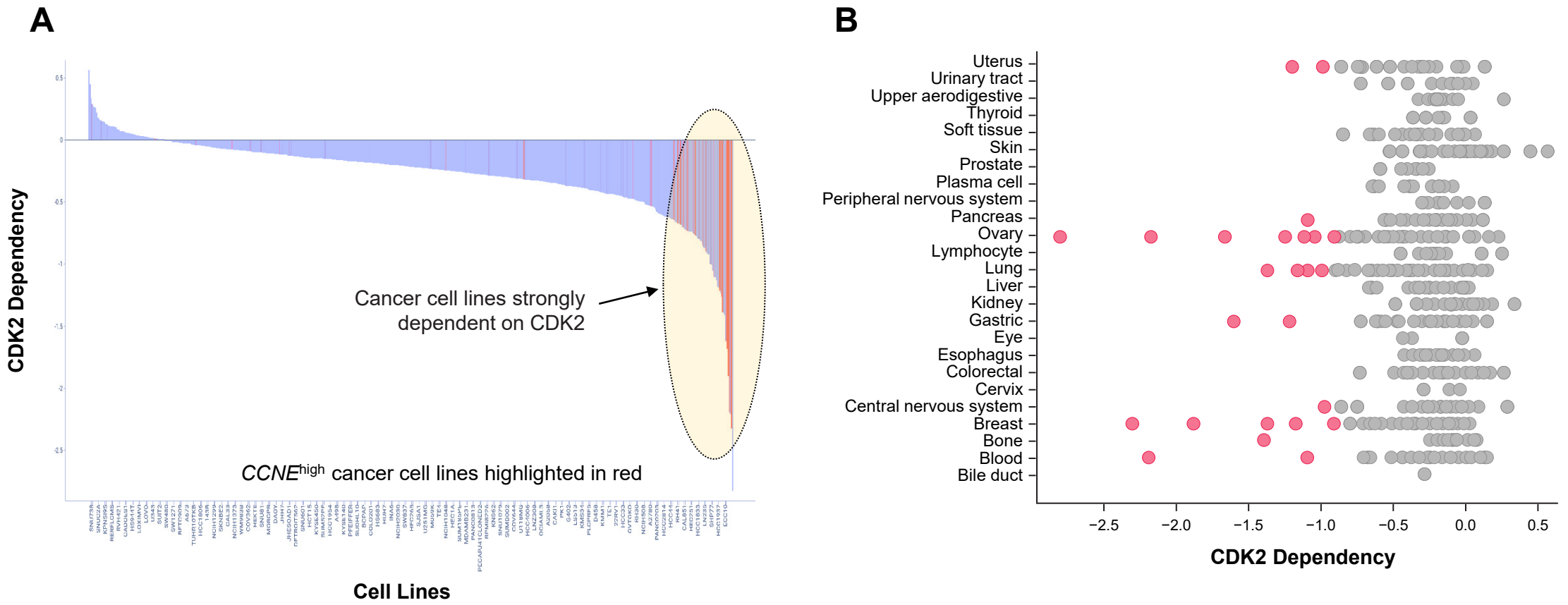
Project Achilles data from the DepMap portal indicate most CDK2-dependent cancer cell lines harbor *CCNE1* amplification or overexpression across multiple lineages



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

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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

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

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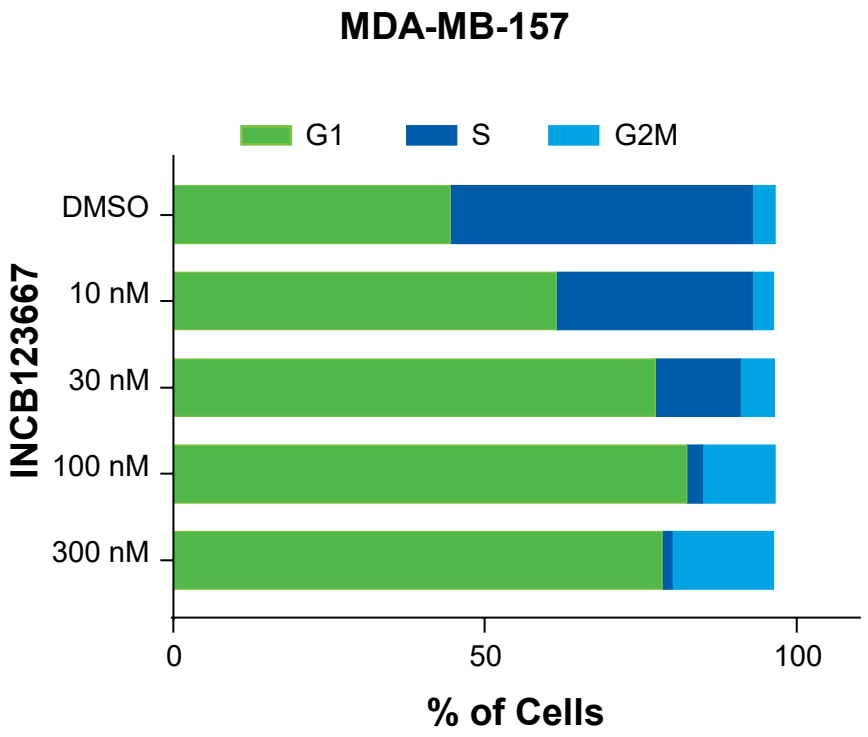

INCB123667 induces senescence in *CCNE1*^{high} cells

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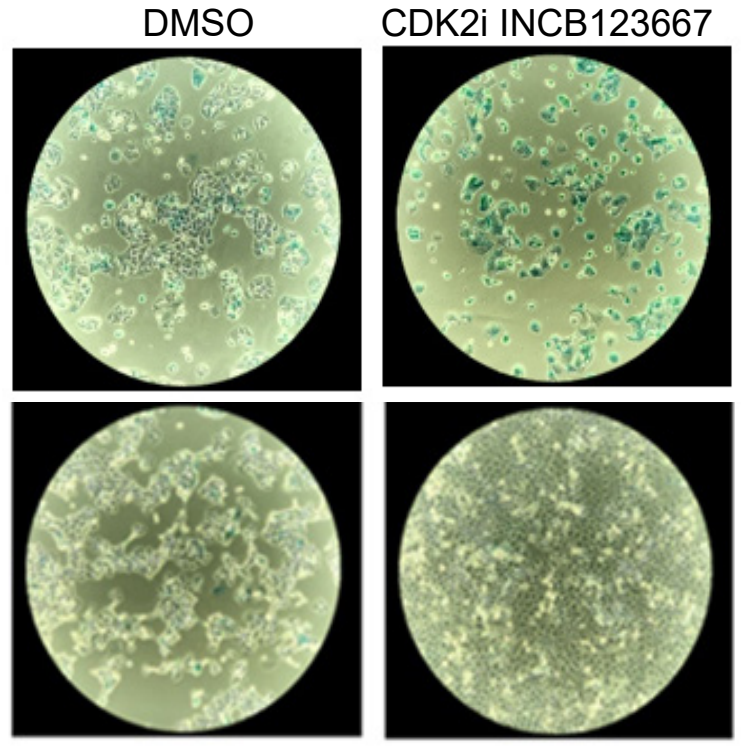

Senescence demonstrated by beta-galactosidase (SA-βgal) staining

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

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

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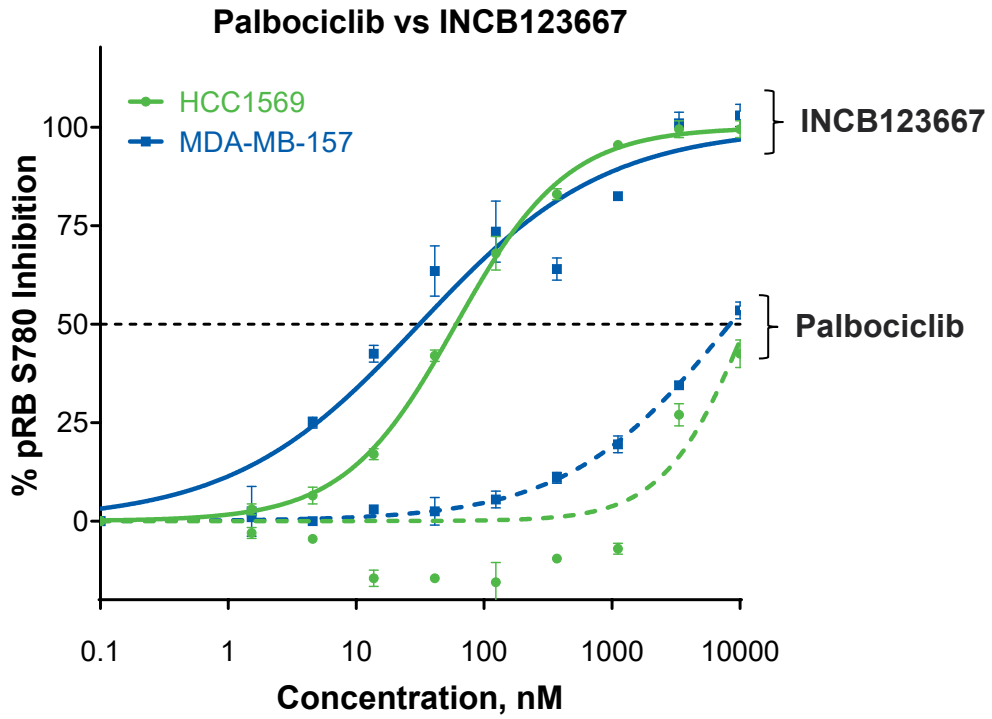

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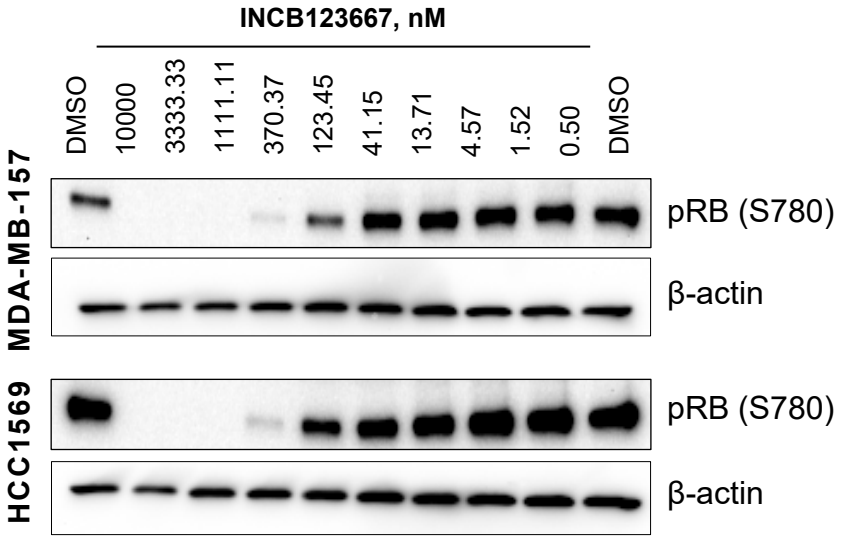

DMSO, dimethyl sulfoxide; pRB, phosphorylated retinoblastoma protein.

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

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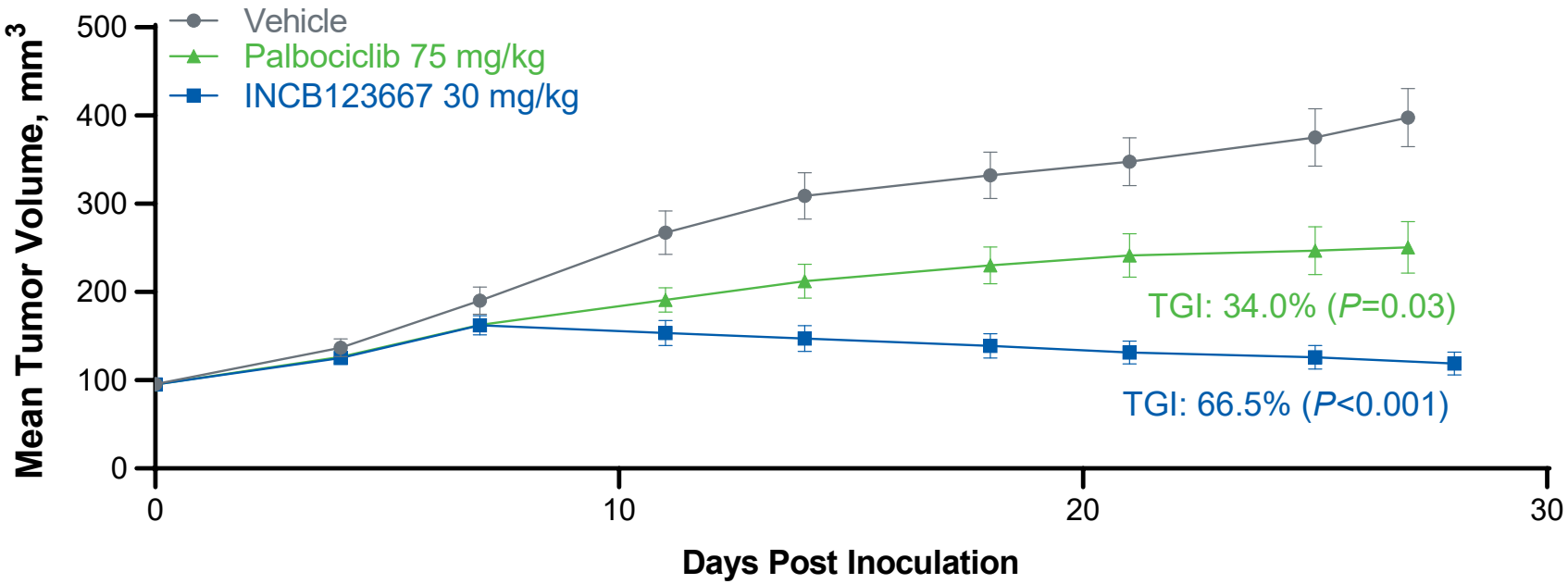
INCB123667 inhibited tumor growth by 66.5% (*P*<0.001) vs a tumor growth inhibition (TGI) of 34% by palbociclib in an HR$^-$/HER2$^+$ epithelial breast cancer line HCC1569 xenograft model in NSG/SCID mice



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

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

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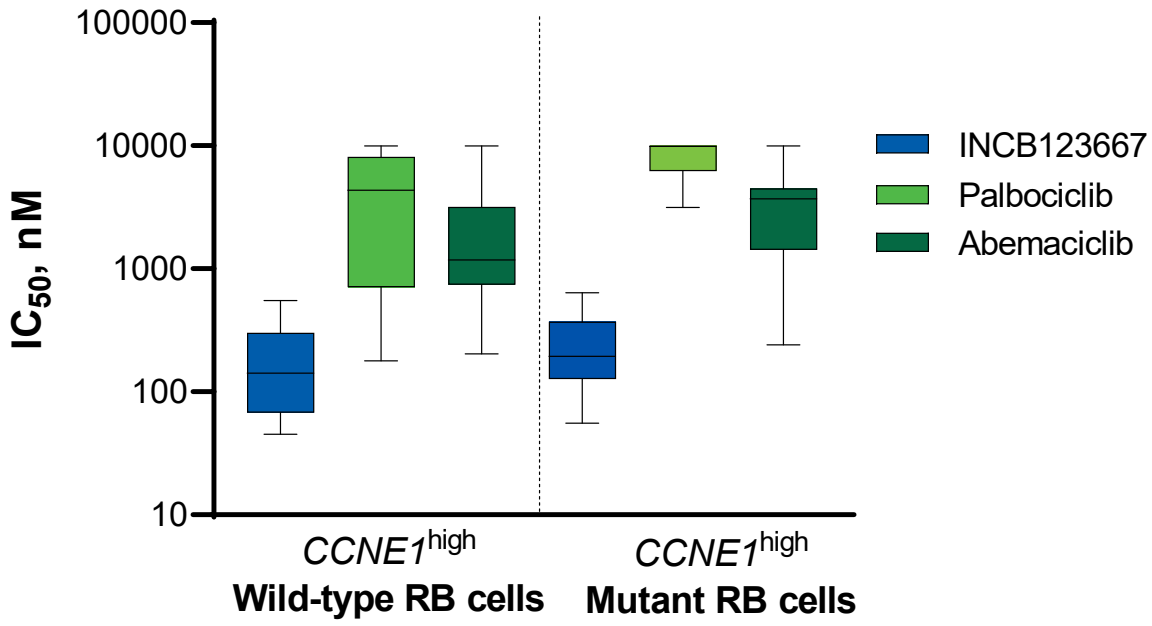

Cyclin E1/CDK2 remains active in RB-mutant *CCNE1*^{high} tumor cells

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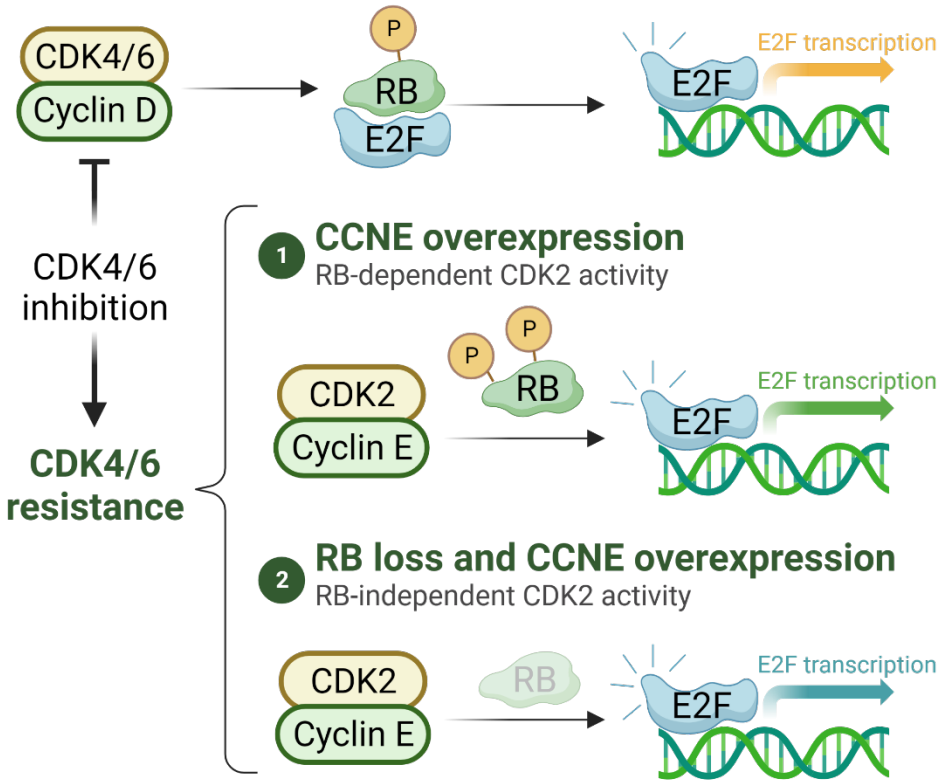

IC$_{50}$, half-maximal inhibitory concentration; RB, retinoblastoma protein.

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

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

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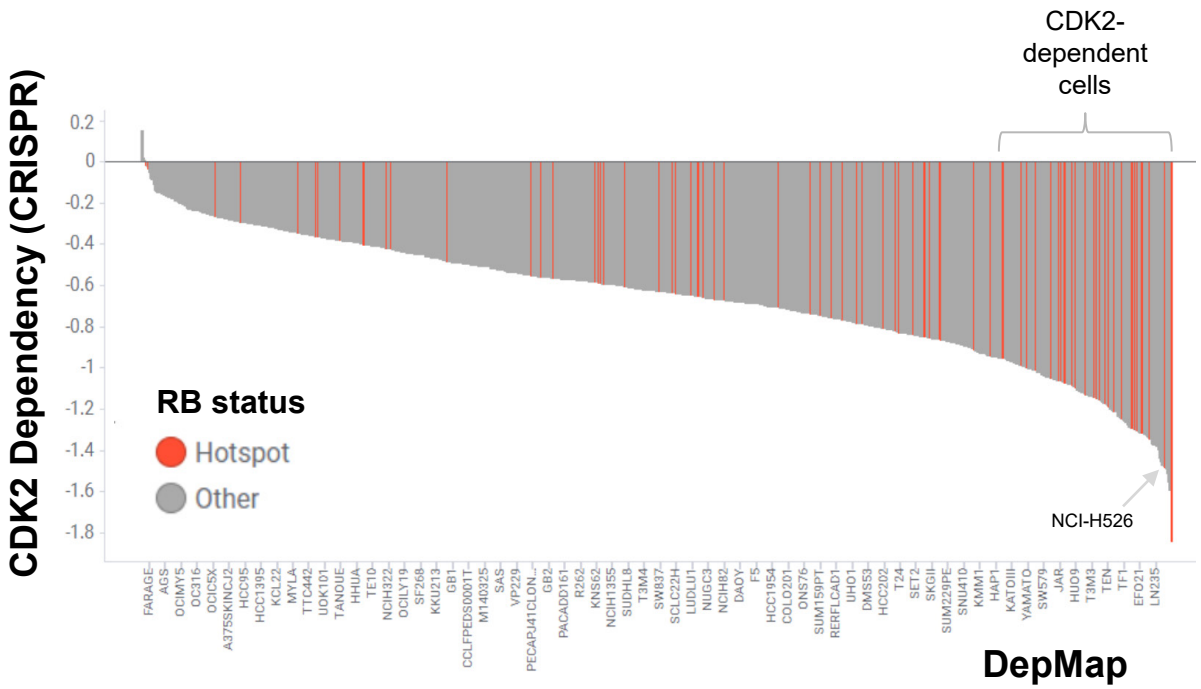

INCB123667 inhibits tumor growth in NCI-H526 RB-mutant in vivo tumor model

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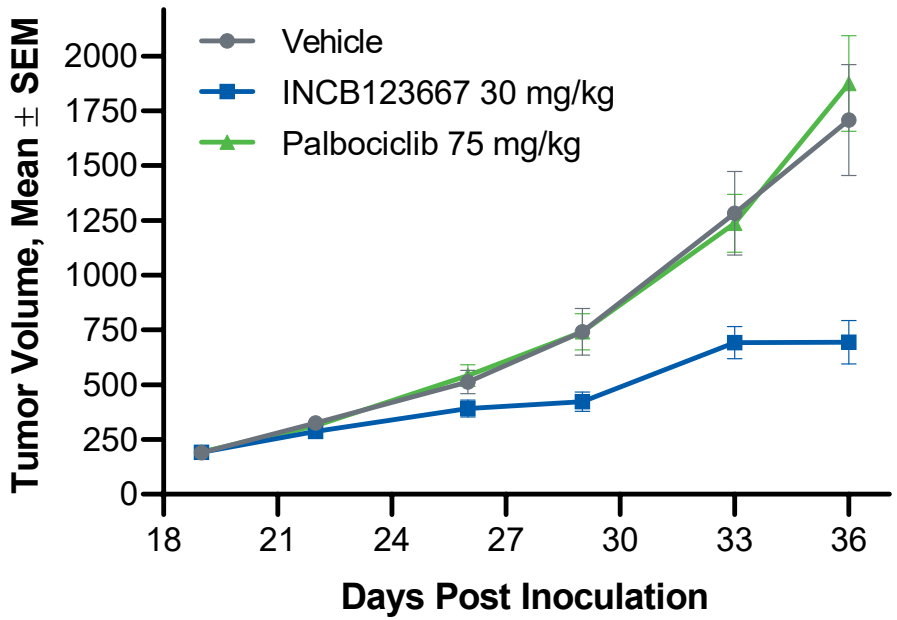

RB, retinoblastoma protein; SEM, standard error of the mean.
Source: Broad Institute. DepMap. https://depmap.org/portal/.

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

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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.

Summary

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- 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.

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