Rational Design of Selective CDK2 and Cyclin E1 MGDs

Targeted Protein Degradation and Induced Proximity Summit

Nina ILIC-WIDLUND

Boston, MA - October 29, 2024

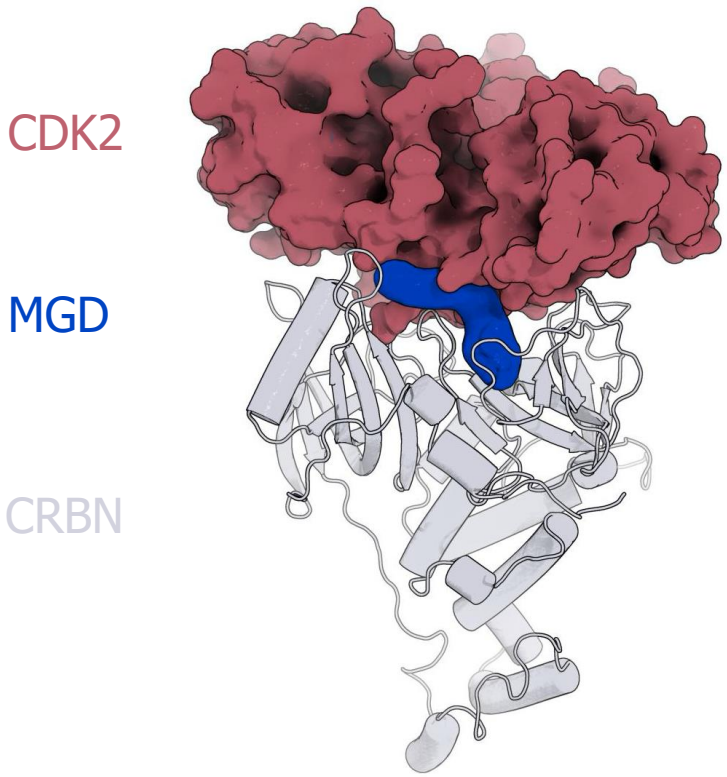
Monte Rosa Therapeutics

Forward-Looking Statements

This communication includes express and implied "forward-looking statements," including forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements include all statements that are not historical facts and, in some cases, can be identified by terms such as "may," "might," "will," "could," "would," "should," "expect," "intend," "plan," "objective," "anticipate," "believe," "estimate," "predict," "potential," "continue," "ongoing," or the negative of these terms, or other comparable terminology intended to identify statements about the future. Forward-looking statements contained herein include, but are not limited to, statements about our ability to grow our product pipeline, statements around the Company's QuEEN™ discovery engine and the Company's view of its potential to identify degradable protein targets and rationally design MGDs with unprecedented selectivity, statements around the productivity of the QuEEN discovery engine and the potential of the Company's MGDs against a broad spectrum of targets, statements about the advancement and timeline of our preclinical and clinical programs, pipeline and the various products therein, including (i) our ongoing clinical development of our GSPT1 degrader referred to as MRT-2359, including our expectations for the nature, significance, and timing for our disclosure of any updated data from our Phase 1/2 clinical trial of MRT-2359 in MYC-driven solid tumors in the second half of 2024, timing for our identification and any disclosure of a recommended Phase 2 dose for MRT-2359 in the second half of 2024, and timing of enrollment of Phase 2 expansion cohorts in the second half of 2024, (ii) the ongoing development of our VAV1-directed degrader, referred to as MRT-6160, including the ongoing Phase 1 SAD/MAD study and the expected timing of disclosure initial clinical data expected in the first quarter of 2025, our expectations of indications for our Phase 2 POC studies for MRT-6160, including the relevance of preclinical data for such indications, the timing for initiation of our Phase 2 studies, and our expectations regarding the potential clinical benefit for MRT-6160, (iii) the ongoing development of our NEK7-directed MGD, referred to as MRT-8102, and our expectations around its potential across neurologic indications amongst others, as well as potential use in gout, pericarditis, and other peripheral inflammatory conditions, including our expectations to submit an IND to the FDA in the first quarter of 2025, and our statements around multiple anticipated clinical readouts, including results from proof-of-concept patient studies for MRT-2359, MRT-6160, and MRT-8102, advancement and application of our pipeline, including identification and the timing thereof of a development candidate for CDK2 until the end of 2024, statements around the advancement and application of our platform, statements concerning our expectations regarding our ability to nominate and the timing of our nominations of additional targets, product candidates, and development candidates, statements regarding regulatory filings for our development programs, including the planned timing of such regulatory filings, such as IND applications, and potential review by regulatory authorities, our use of capital, expenses and other financial results in the future, availability of funding for existing programs, ability to fund operations into the first half of 2027, as well as our expectations of success for our programs, strength of collaboration relationships and the strength of our financial position, among others. By their nature, these statements are subject to numerous risks and uncertainties, including those risks and uncertainties set forth in our most recent Annual Report on Form 10-K for the year ended December 31, 2023, filed with the U.S. Securities and Exchange Commission on March 14, 2024, and any subsequent filings, that could cause actual results, performance or achievement to differ materially and adversely from those anticipated or implied in the statements. You should not rely upon forward-looking statements as predictions of future events. Although our management believes that the expectations reflected in our statements are reasonable, we cannot guarantee that the future results, performance, or events and circumstances described in the forward-looking statements will be achieved or occur. Recipients are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date such statements are made and should not be construed as statements of fact. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, any future presentations, or otherwise, except as required by applicable law. Certain information contained in these materials and any statements made orally during any presentation of these materials that relate to the materials or are based on studies, publications, surveys and other data obtained from third-party sources and our own internal estimates and research. While we believe these third-party studies, publications, surveys and other data to be reliable as of the date of these materials, we have not independently verified, and make no representations as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, no independent source has evaluated the reasonableness or accuracy of our internal estimates or research and no reliance should be made on any information or statements made in these materials relating to or based on such internal estimates and research. These materials remain the proprietary intellectual property of Monte Rosa Therapeutics and should not be distributed or reproduced in whole or in part without the prior written consent of Monte Rosa Therapeutics.

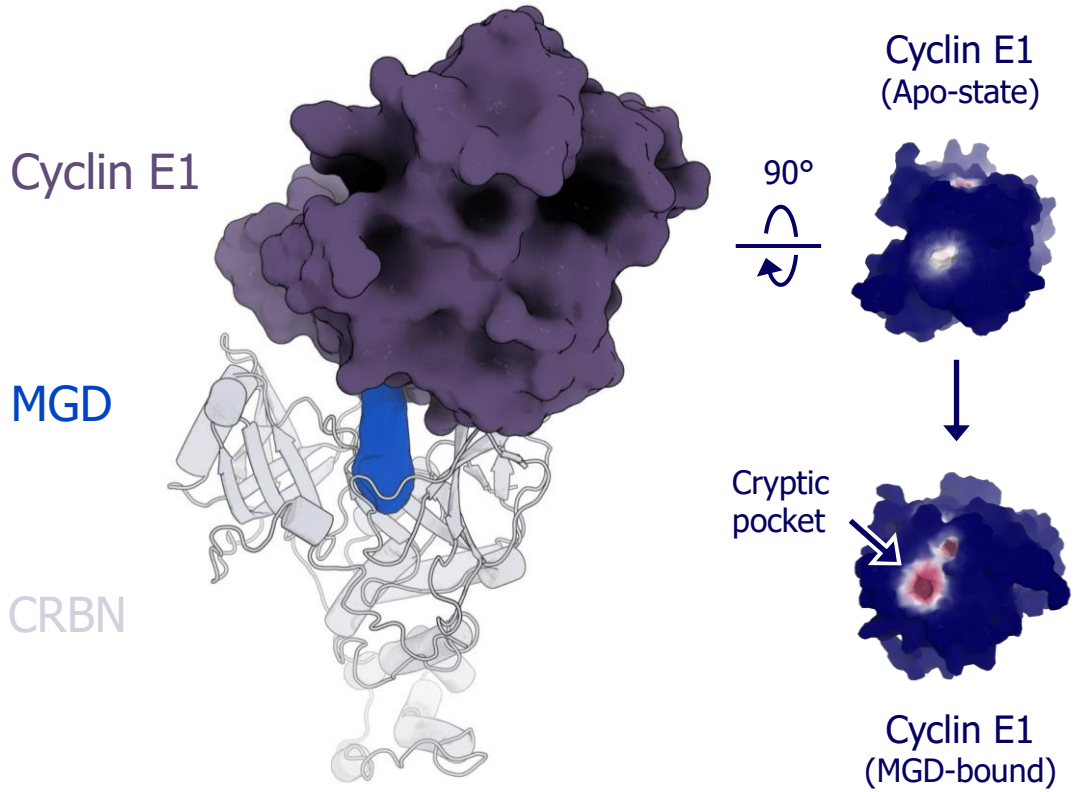
Targeting the Cell Cycle by Exquisitely Selective Molecular Glues Degraders

CDK2 program: Novel binding mode (not G-loop engagement) and differentiated MoA over inhibitors



CDK2-MGD-CRBN-DDB1 cryo-EM structure
(DDB1 not shown)

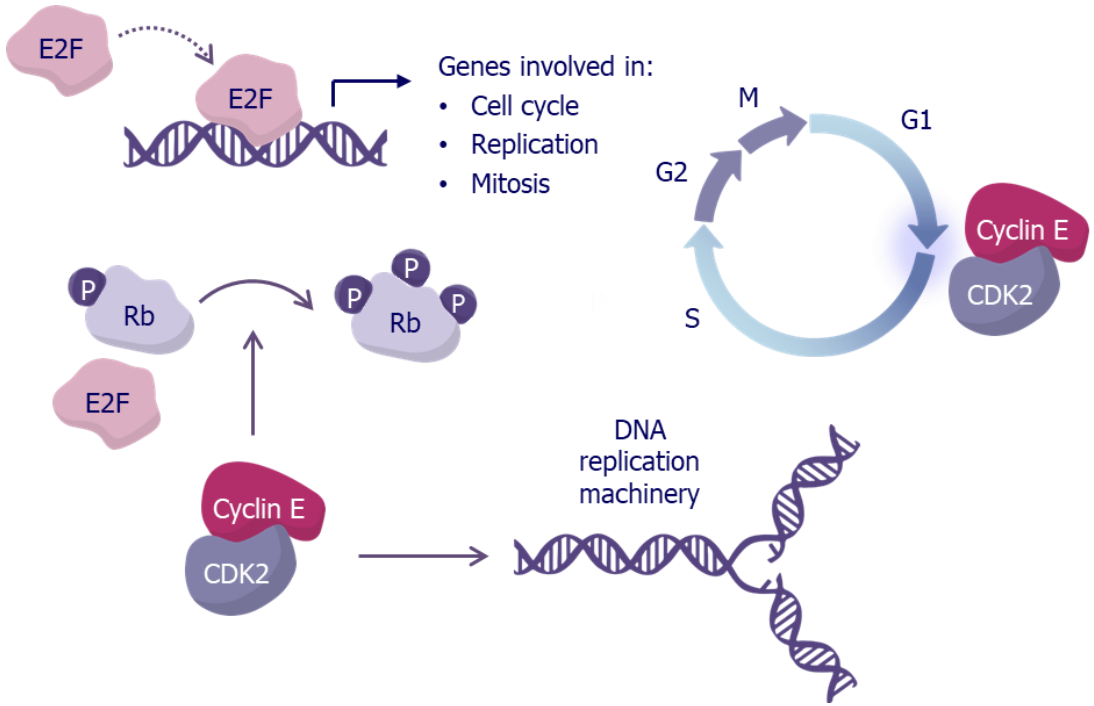
Cyclin E1 program: Novel binding mode leveraging a cryptic pocket on cyclin E1



CCNE1-MGD-CRBN-DDB1 cryo-EM structure
(DDB1 not shown)

Cyclin E and CDK2 Play Critical Roles in Cell Cycle Regulation, Tumorigenesis, and Drug Response

Cyclin E and CDK2 are critical regulators of G1-S progression



Cancers with cyclin E/CDK2 dysregulation

- **CDK2 program**: HR^{+} breast cancer where CDK2 activity reduces response to CDK4/6 inhibitors
- **Cyclin E1 program**: Cyclin E1 (*CCNE1*) amplified cancers (ovarian, endometrial, gastric, breast, etc.)

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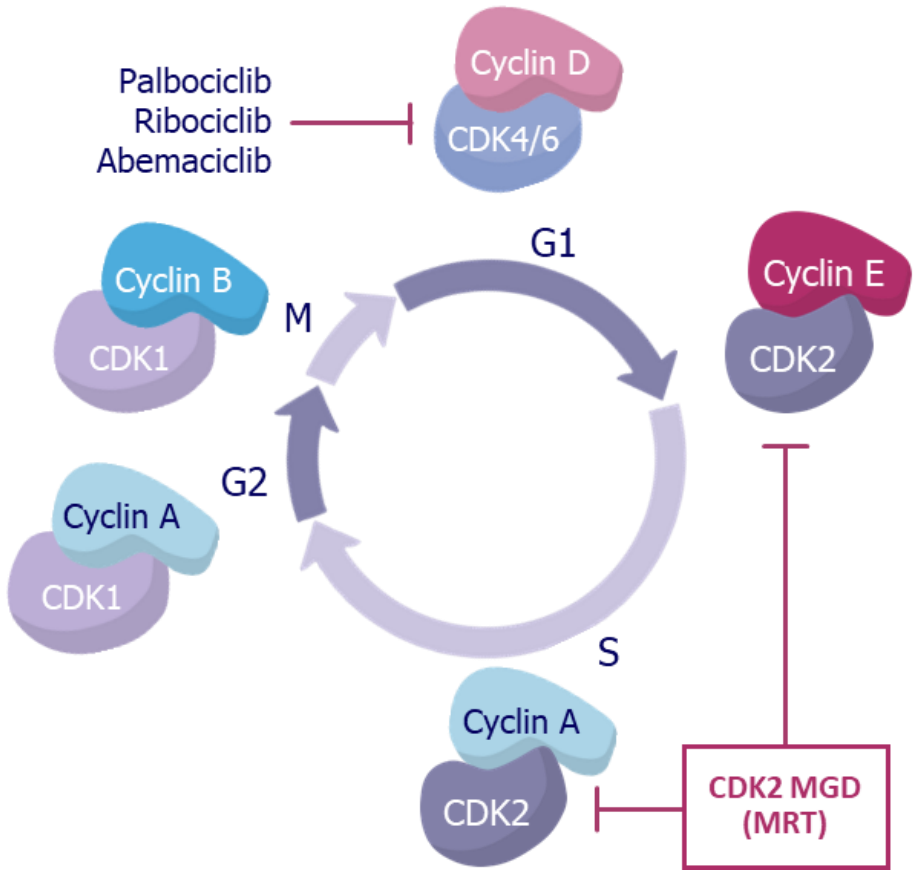
CDK2 Program

CDK2 is a Key Driver of Cell Cycle Progression in Cancer

CDK2: a key cell cycle regulator



Therapeutic hypothesis:

- CDK2 is a key driver of cancers with cyclin dependent kinase pathway alterations
- MGDs will achieve greater selectivity against other CDKs and kinases in general, as well as more sustained pathway inhibition compared to inhibitors

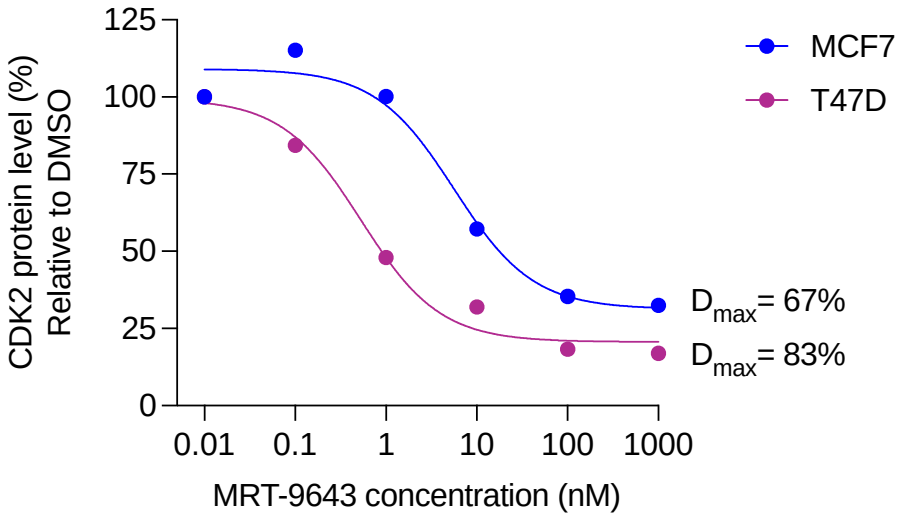
Clinical Opportunity:

- ER positive breast cancer pre and post treatment with CDK4/6 inhibitors (~474K patients)

Patient diagnosed incidence #s, major markets (US, EU and JP): Decision Resources Group (DRG)

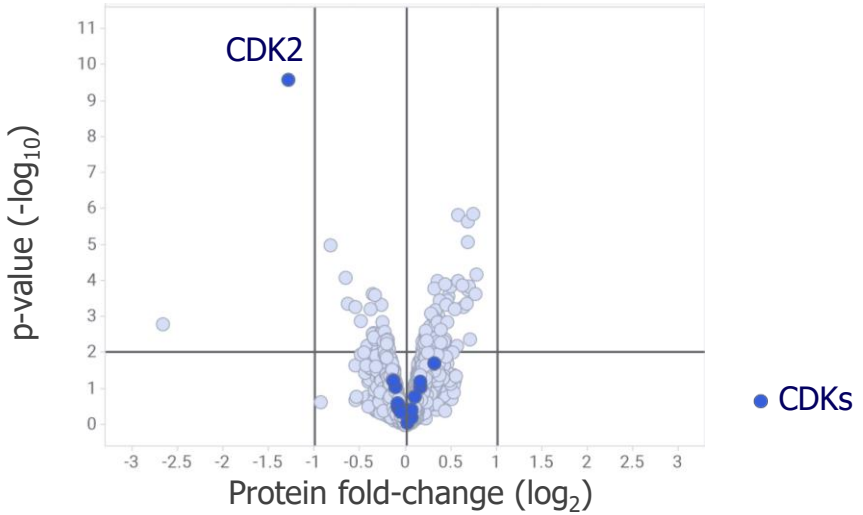
MRT-9643 is a Potent and Highly Selective CDK2-directed MGD

MRT-9643 is a potent CDK2-directed MGD



in vitro data	
CRBN binding, IC_{50}	289 nM
Ternary complex, EC_{50}	6 nM
Degradation, DC_{50} / D_{max} (HEK 293)	56 nM / 64 %

MRT-9643 induces highly selective CDK2 degradation and has a favorable ADME/DMPK profile



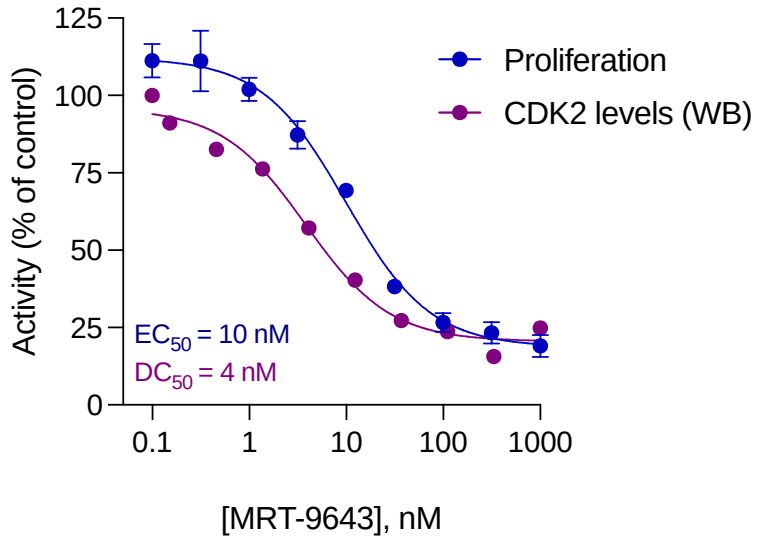
TMT Proteomics (24 hr/1 μM), MCF7 cells

No degradation of other known CRBN neosubstrates

ADMET profile	
CYP DDIs	IC_{50} 15 - >50 μM
hERG inhibition patch clamp	EC_{50} 4.4 μM
Oral bioavailability (mouse)	44 %

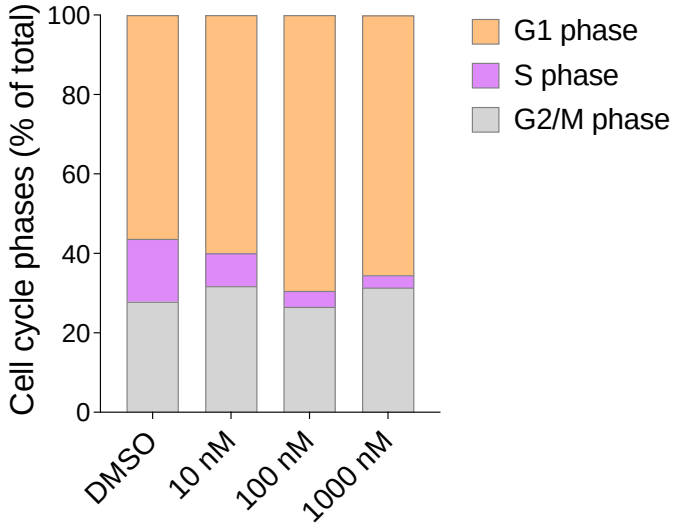
MRT-9643 Inhibits Proliferation of CDK2-dependent Cancer Cells

CDK2 degradation inhibits proliferation



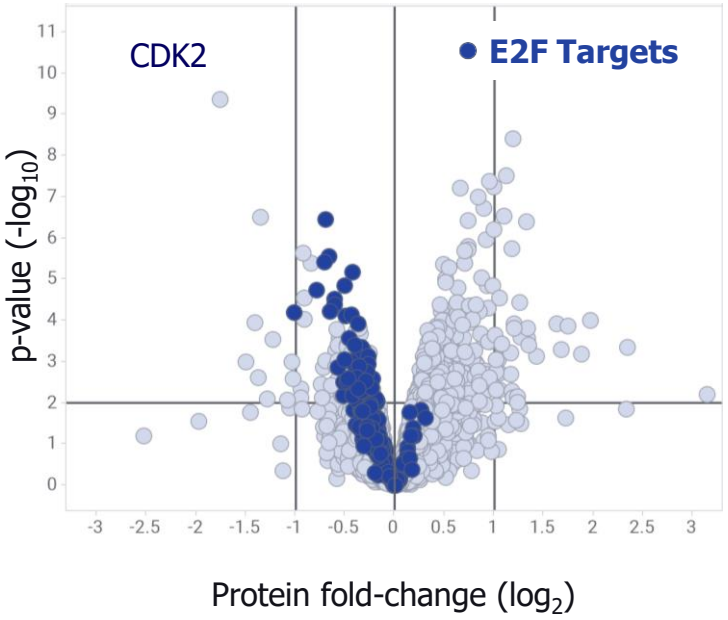
WB degradation (24 hr) MDA-MB-157
CyQuant proliferation assay (7 d) MDA-MB-157

CDK2 degradation arrests CDK2-dependent cells in G1 phase



Cell cycle analysis (DAPI and EdU)
MDA-MB-157 (24 hr)

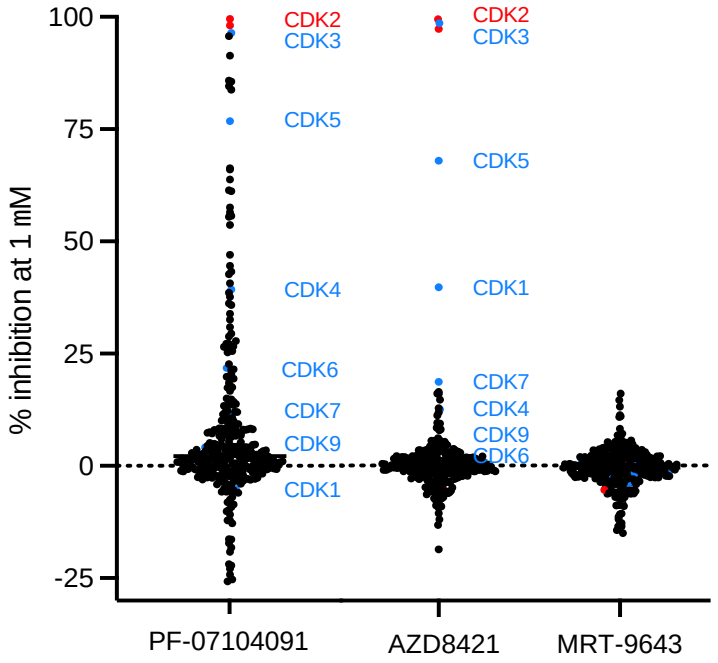
CDK2 degradation results in reduction of E2F pathway proteins



TMT Proteomics (24 hr/1μM)
MDA-MB-157

MRT-9643 Displays Superior Selectivity Compared to Clinical CDK2 Inhibitors

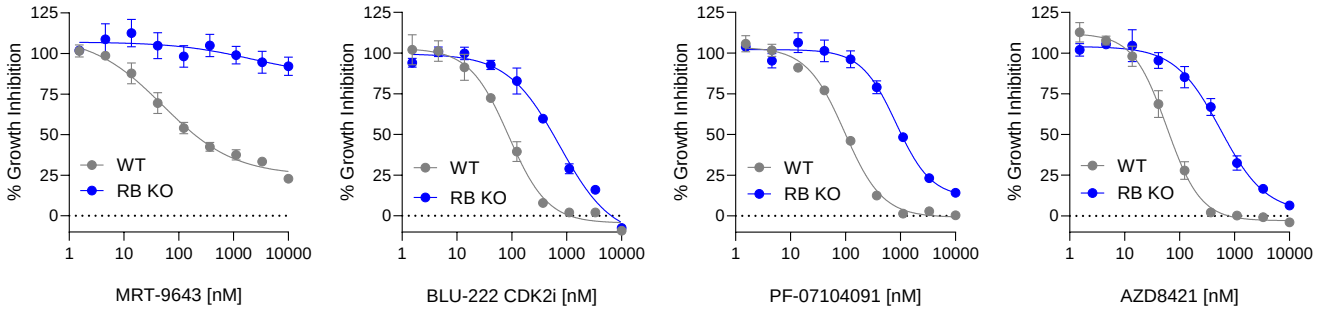
Clinical-stage CDK2 inhibitors show off target activity in biochemical kinome profiling



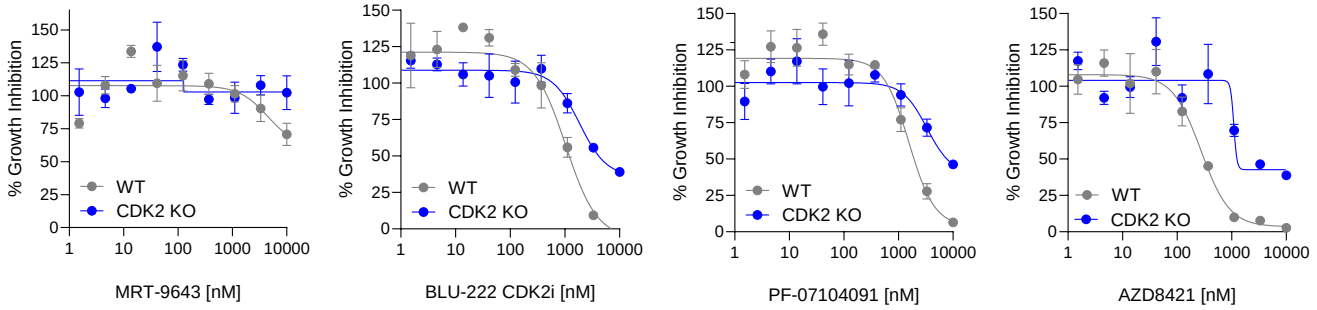
Carna Mobility Shift Assay; 1 µM CDK2i or CDK2 MGD across 323 human kinases

CDK2 inhibitors but not CDK2 MGD display CDK2-independent activity

CDK2-dependent MDA-MB-157 cells – **RB** WT vs. KO



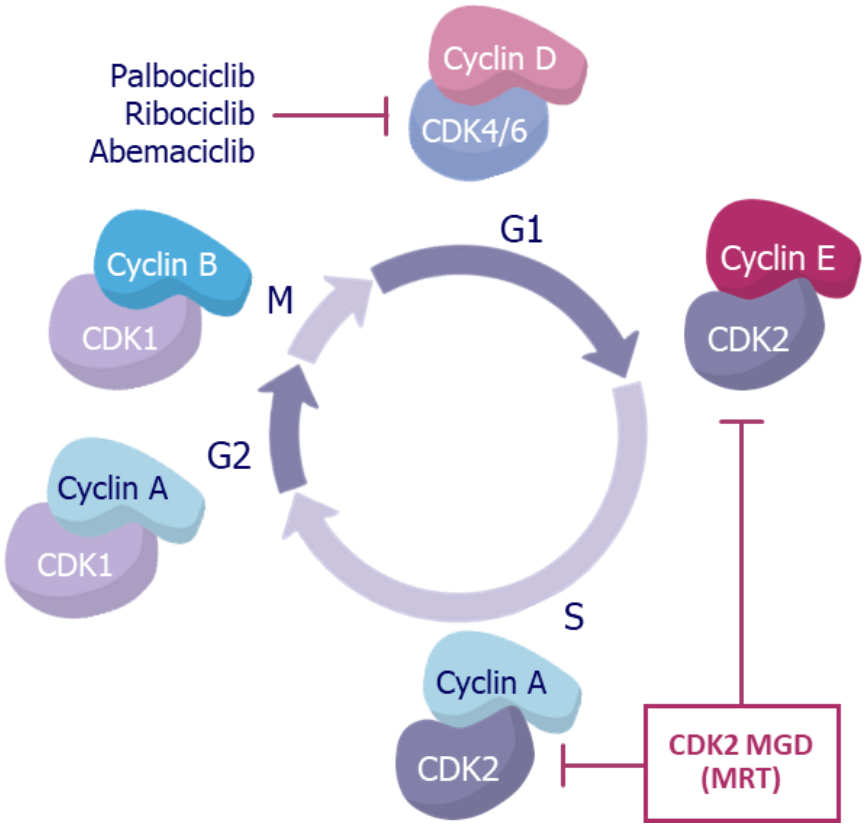
CDK2-independent MCF7 cells – **CDK2** WT vs. KO



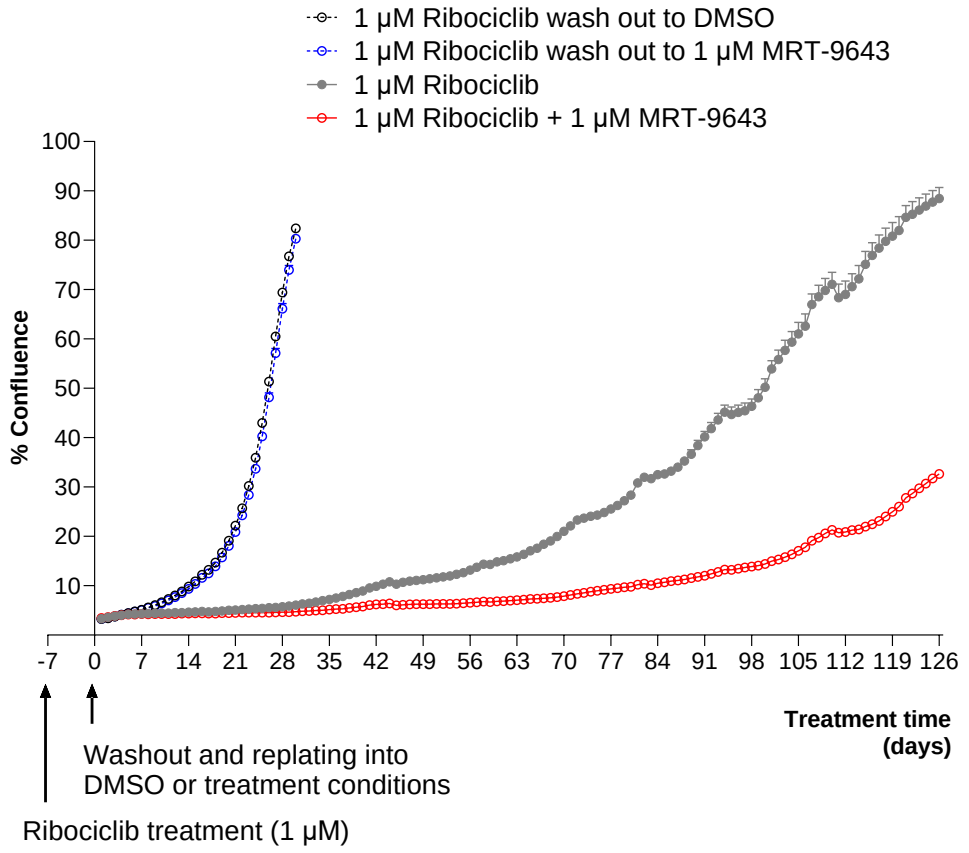
7-day CyQuant assay

MRT-9643/Ribociclib Combination Delays Resistance Onset in ER+ Model *in vitro*

CDK2 MGD and CDK4/6 inhibitor combination



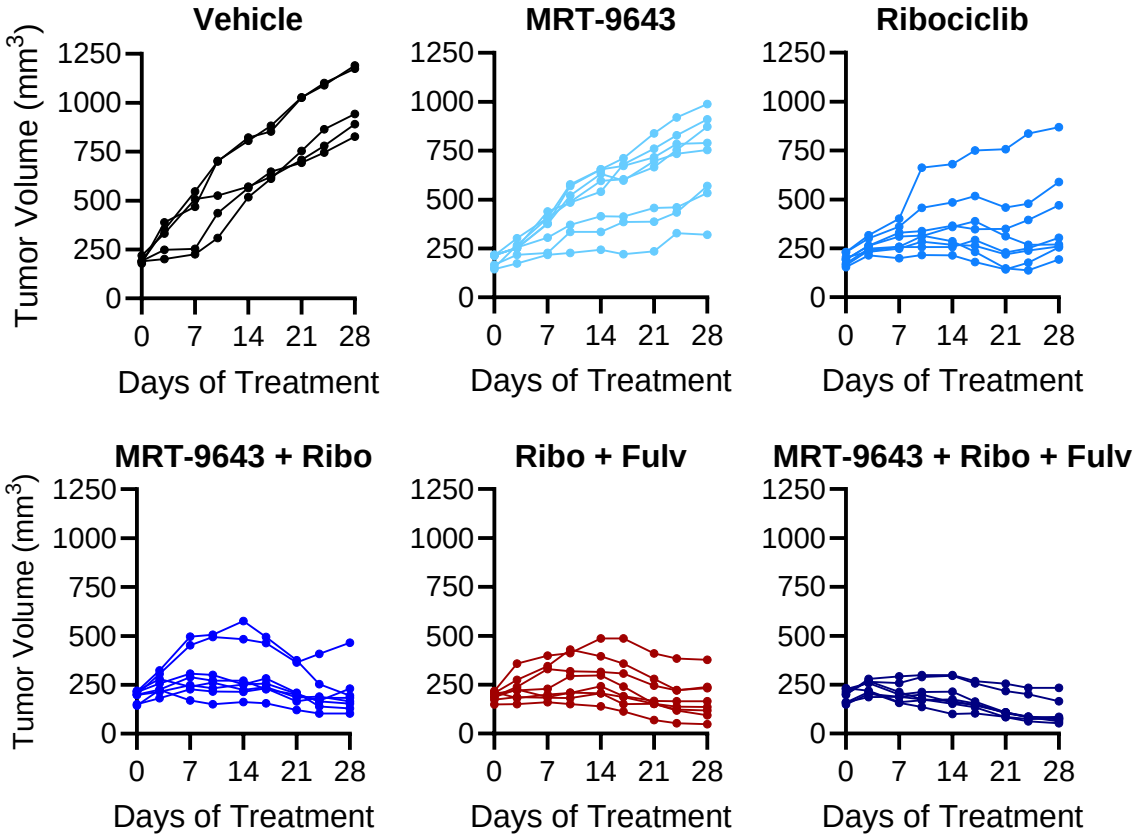
MRT-9643/ribociclib combination delays resistance onset in ER+ model *in vitro*



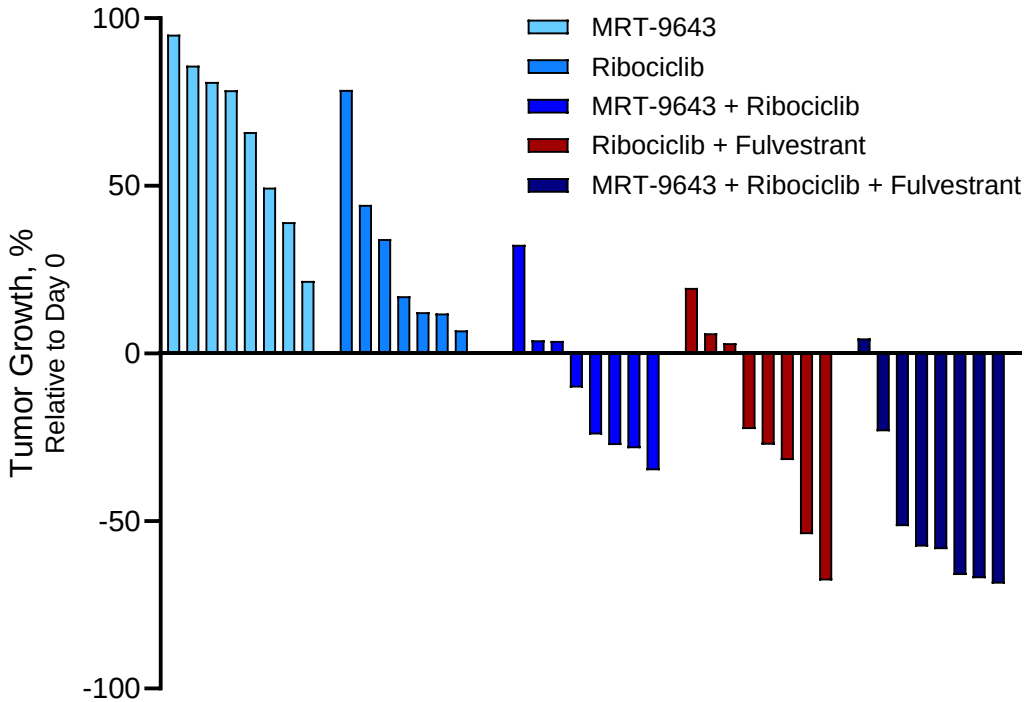
Incucyte confluence monitoring, MCF7

MRT-9643 Demonstrates Activity in Combination with CDK4/6 Inhibitor (and Fulvestrant) in ER+ Breast Cancer (MCF7)

MRT-9643 induces strong TGI in combination with CDK4/6 inhibitor *in vivo*



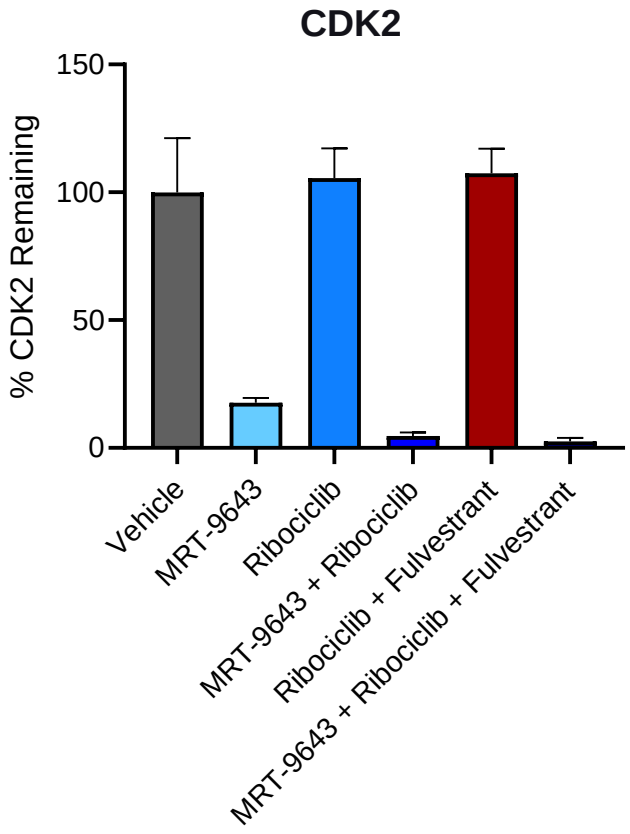
MRT-9643 induces robust tumor regression in combination with CDK4/6 inhibition and fulvestrant

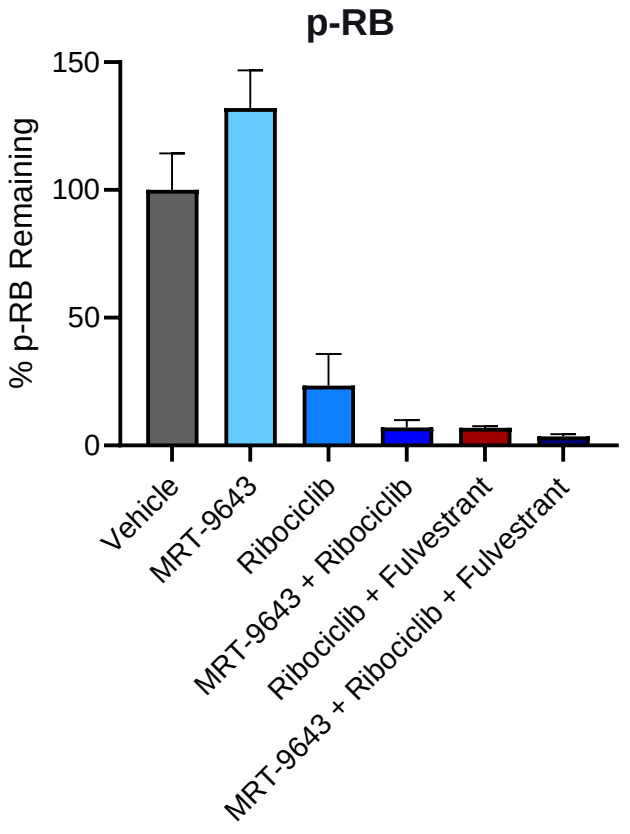


28-day efficacy evaluation in MCF7 CDX Model
(MRT-9643 dosed at 30 mpk BID)

MRT-9643 Induces Strong Pathway Suppression in Combination with CDK4/6 Inhibitor in ER+ Breast Cancer (MCF7)

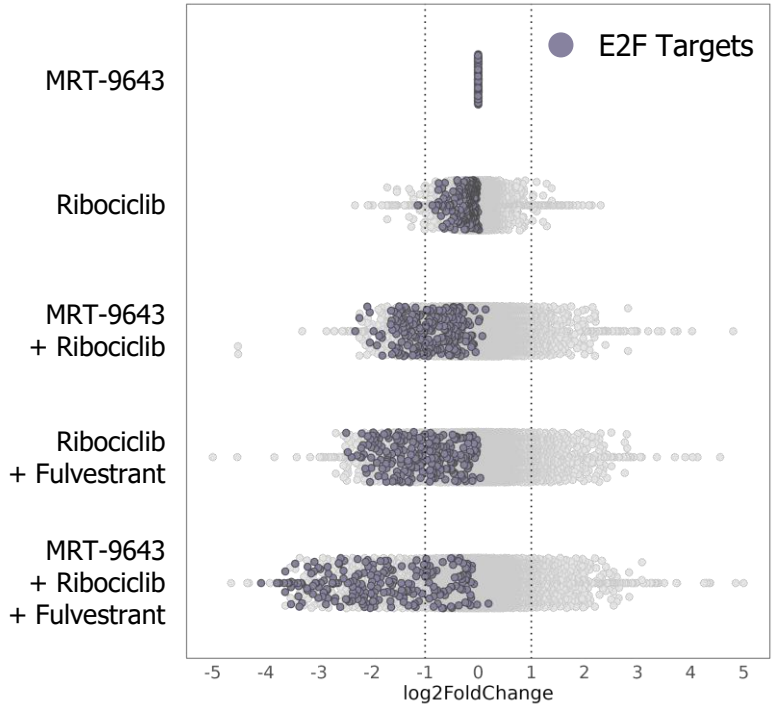
MRT-9643 readily degrades CDK2 *in vivo*, alone or in combination





Western blot analysis
Day 28 PD, 1 hr post second BID dose

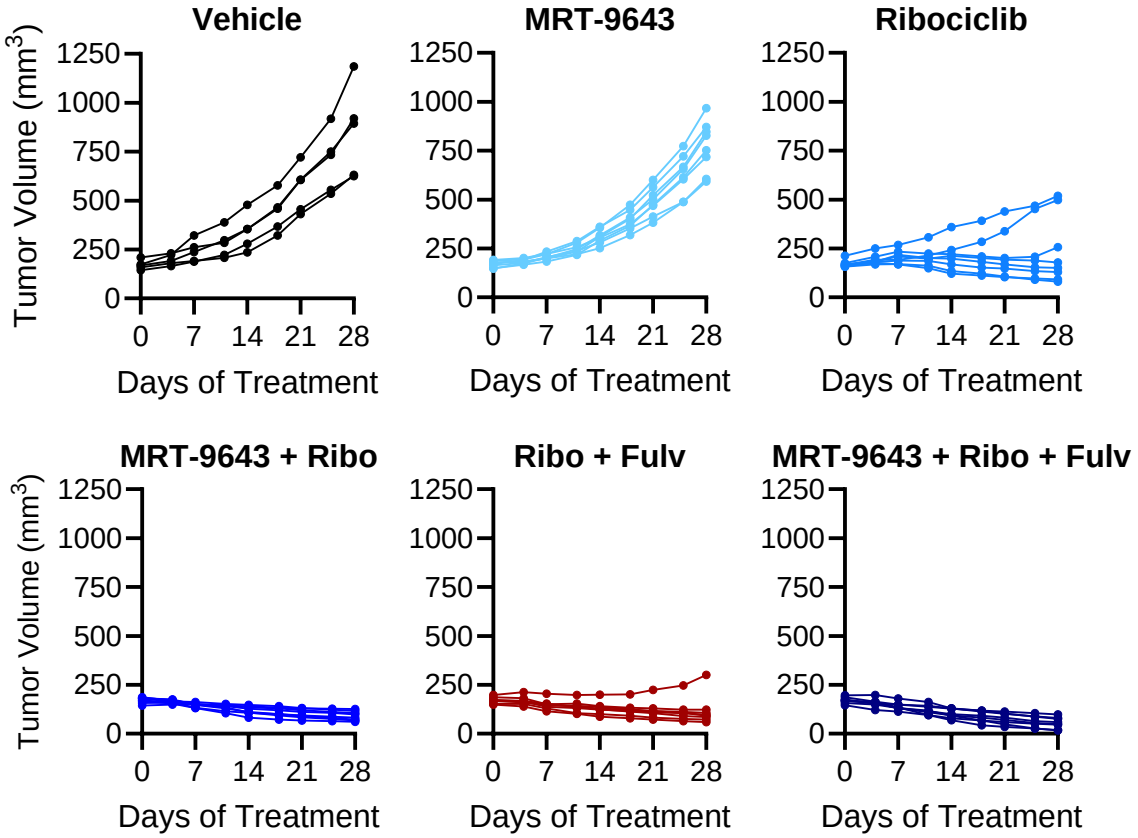
MRT-9643 induces robust pathway suppression in combination with breast cancer SoC



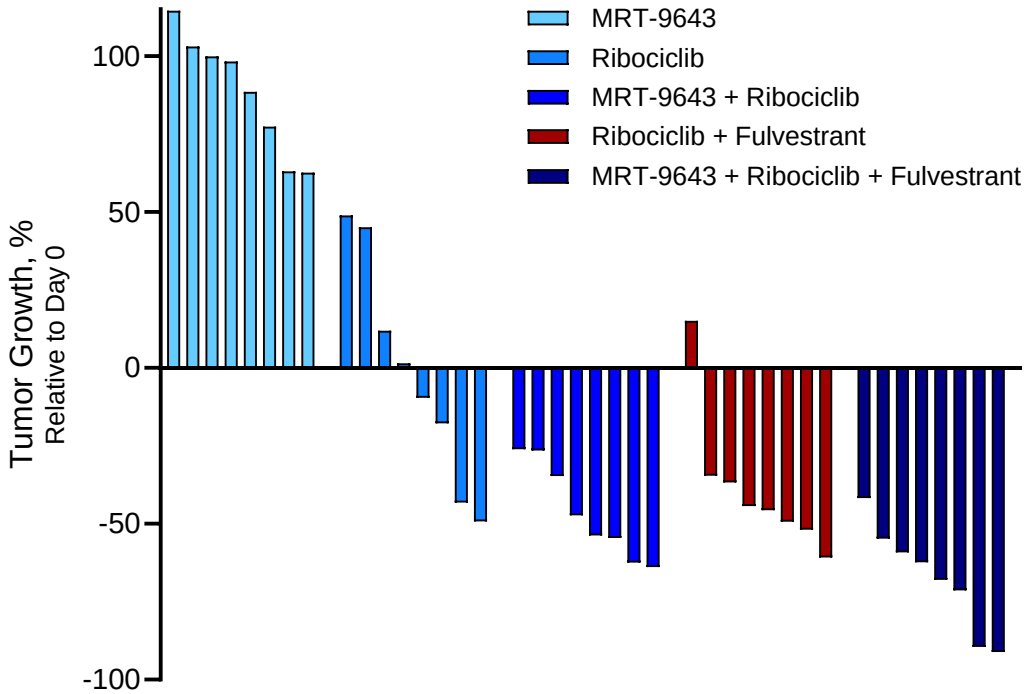
RNA-Seq analysis (fold change relative to vehicle)
Day 28 PD, 1 hr post second BID dose

MRT-9643 Demonstrates Activity in Combination with CDK4/6 Inhibitor in ER+ Breast Cancer (T47D)

MRT-9643 induces strong TGI in combination with CDK4/6 inhibitors *in vivo*



MRT-9643 induces robust tumor regression in combination with CDK4/6 inhibition and fulvestrant



28-day efficacy evaluation in T47D CDX Model
(MRT-9643 dosed at 30 mpk BID)

CDK2 Program

- **Highly selective** CDK2-targeting molecular glue degraders
- Best in CDK2-class potential
- RB-dependent activity indicates on-target effects and differentiates from clinical-stage CDK2 inhibitors
- Efficacy observed in **combination with CDK4/6 inhibitors**; combined effects (PD modulation and efficacy) in $ER^+/HER2^-$ breast cancer xenograft models
- **Program advancing towards development candidate nomination**

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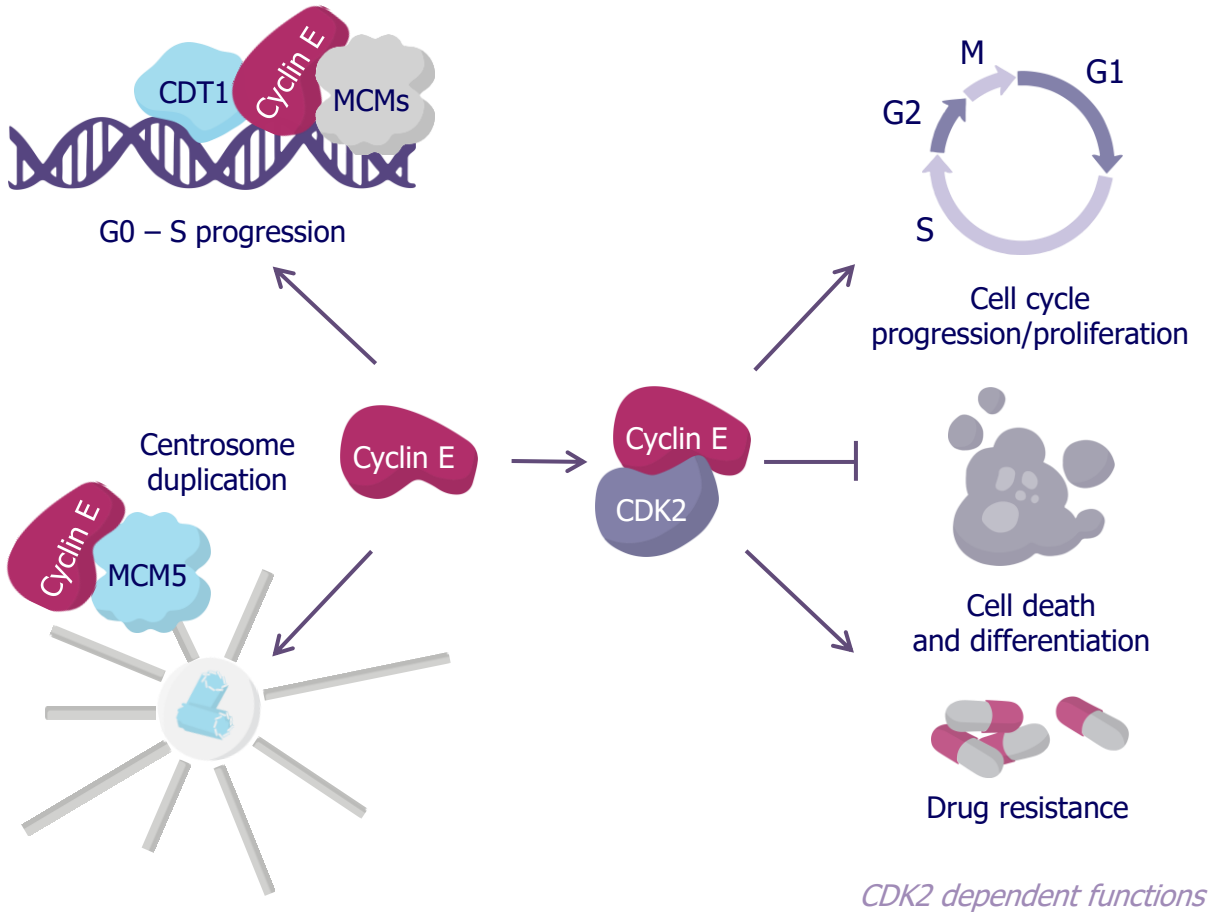
Cyclin E1 Program

CCNE1 (Cyclin E1) is a Target for Solid Tumors with Deregulated Cyclin E1

Cyclin E drives multiple hallmark cancer mechanisms



Therapeutic hypothesis:

CCNE1 (cyclin E1) is a well-recognized human oncogene that drives multiple hallmarks of cancer, and has been considered undruggable

Selective degradation of cyclin E1 can target tumors with deregulated cyclin E1 (amplification or overexpression)

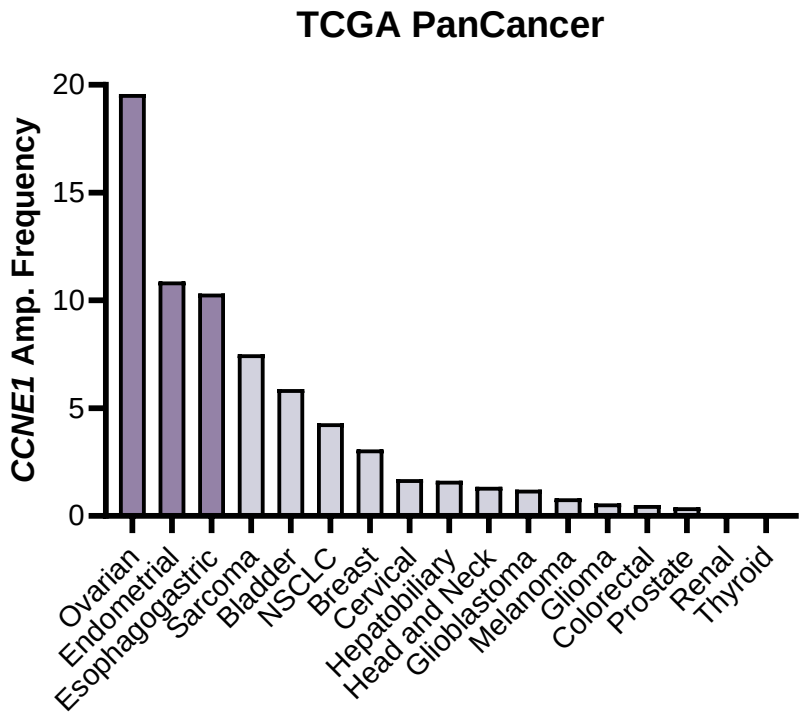
Clinical opportunity:

First-in-class cyclin E1 degraders for cyclin E1 amplified cancers

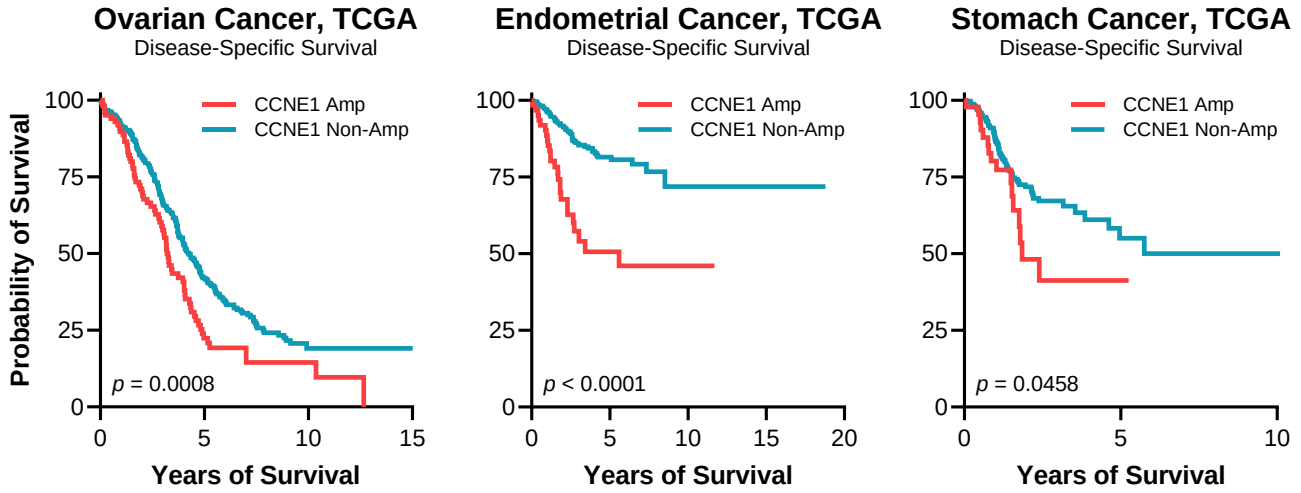
- Ovarian (~19%), endometrial (~10%), gastric (~10%) cancer, and others

CCNE1 is Frequently Amplified and Correlates with Poor Survival

CCNE1 Amplification Across Cancer Types



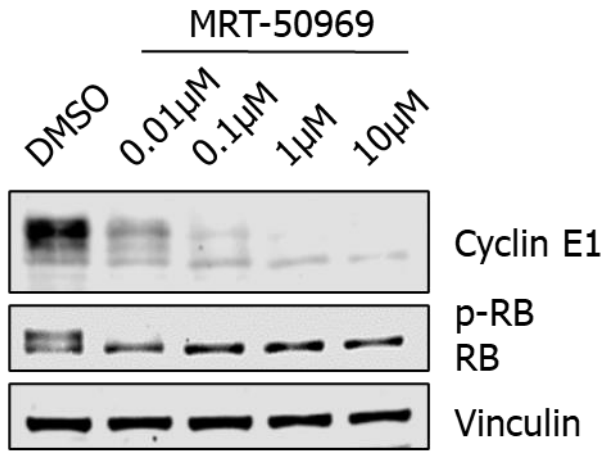
CCNE1 Amplification Correlates with Poor Patient Survival



Cancer	5-Year Survival		CCNE1 Amp. Hazard Ratio
	CCNE1 Amp	Non-Amp	
Ovarian	**22.4%**	42.1%	1.70
Endometrial	**50.6%**	81.4%	7.15
Stomach	**41.2%**	55.0%	1.93

MRT-50969 is a Potent and Highly Selective Cyclin E1-directed MGD

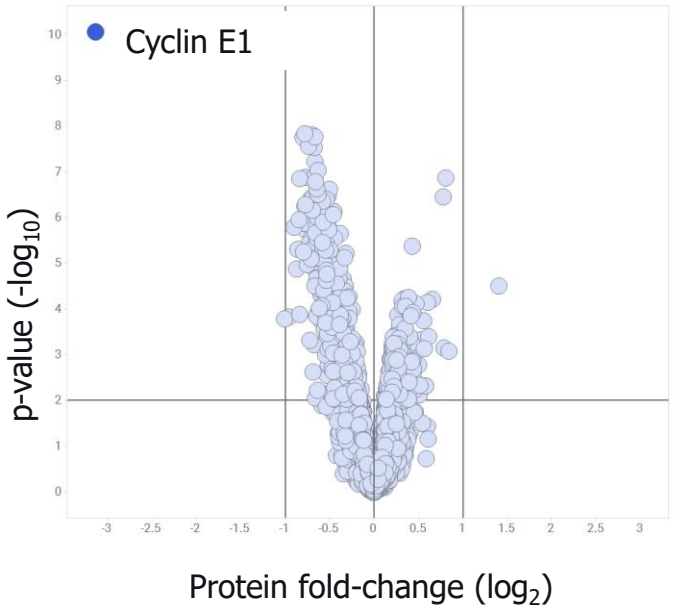
Cyclin E1 degradation leads to downstream pathway suppression



***In vitro* data**	
CRBN binding, IC_{50}	0.15 μM
Ternary complex, EC_{50}	3 nM
Degradation, DC_{50}/D_{max}	3 nM / 94 %

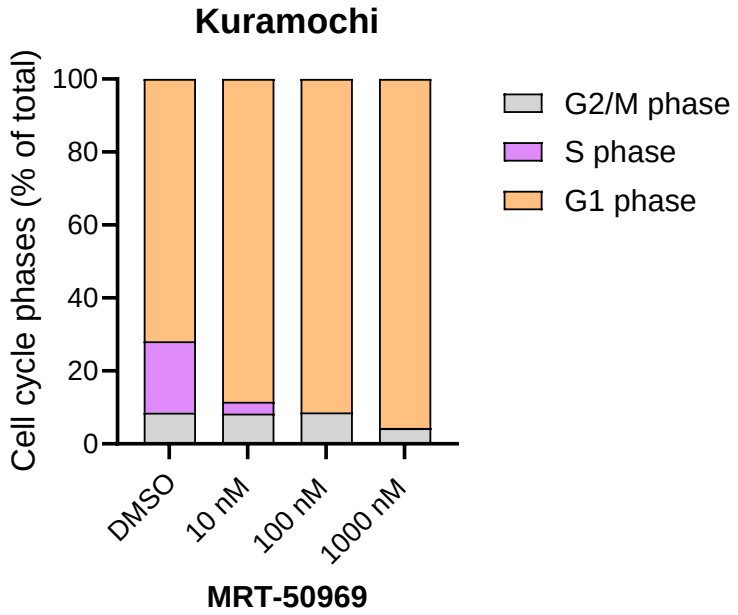
Western blot, OVISE, 24h

MRT-50969 is highly selective for cyclin E1



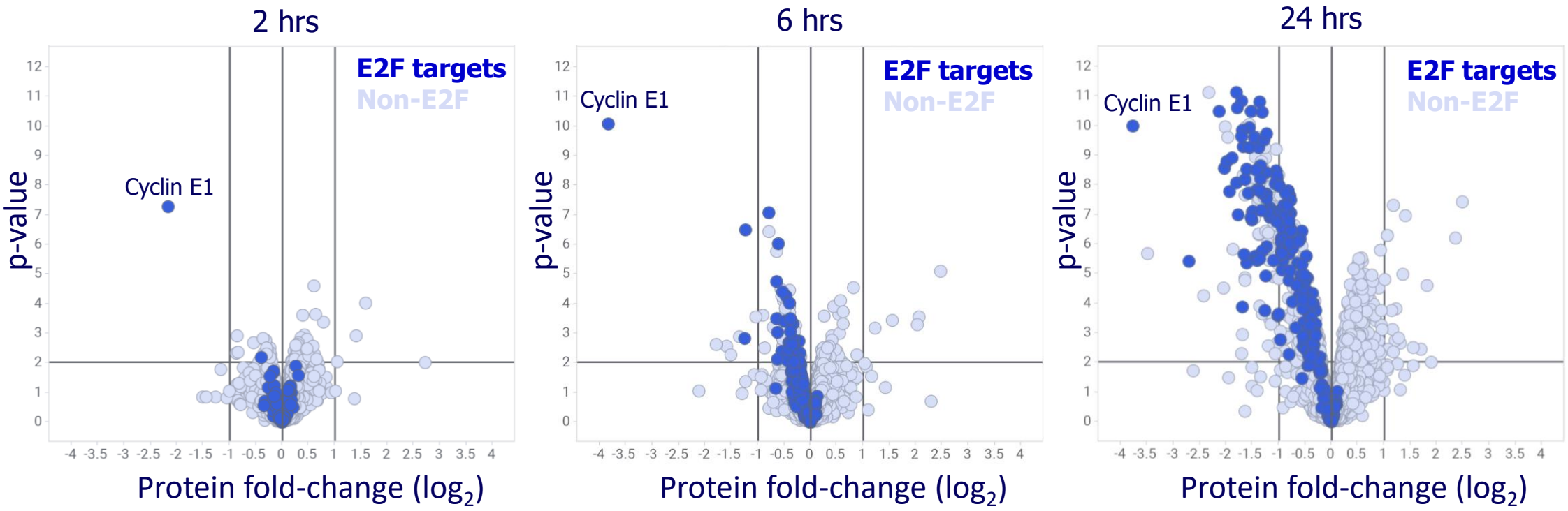
TMT Proteomics, MDA-MB-157 RB K/O
1μM, 24h

MRT-50969 induces robust G1/S cell cycle arrest



FACS, EdU incorporation, 48h

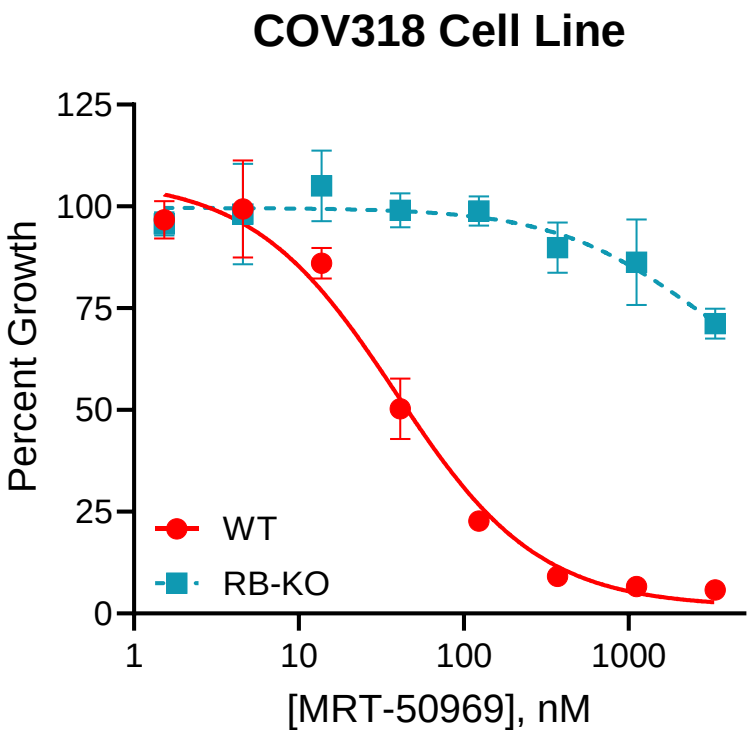
MRT-50969 Suppresses E2F Targets via Cyclin E1 Degradation



TMT proteomics, HCC1569 cells
1μM MRT-50969

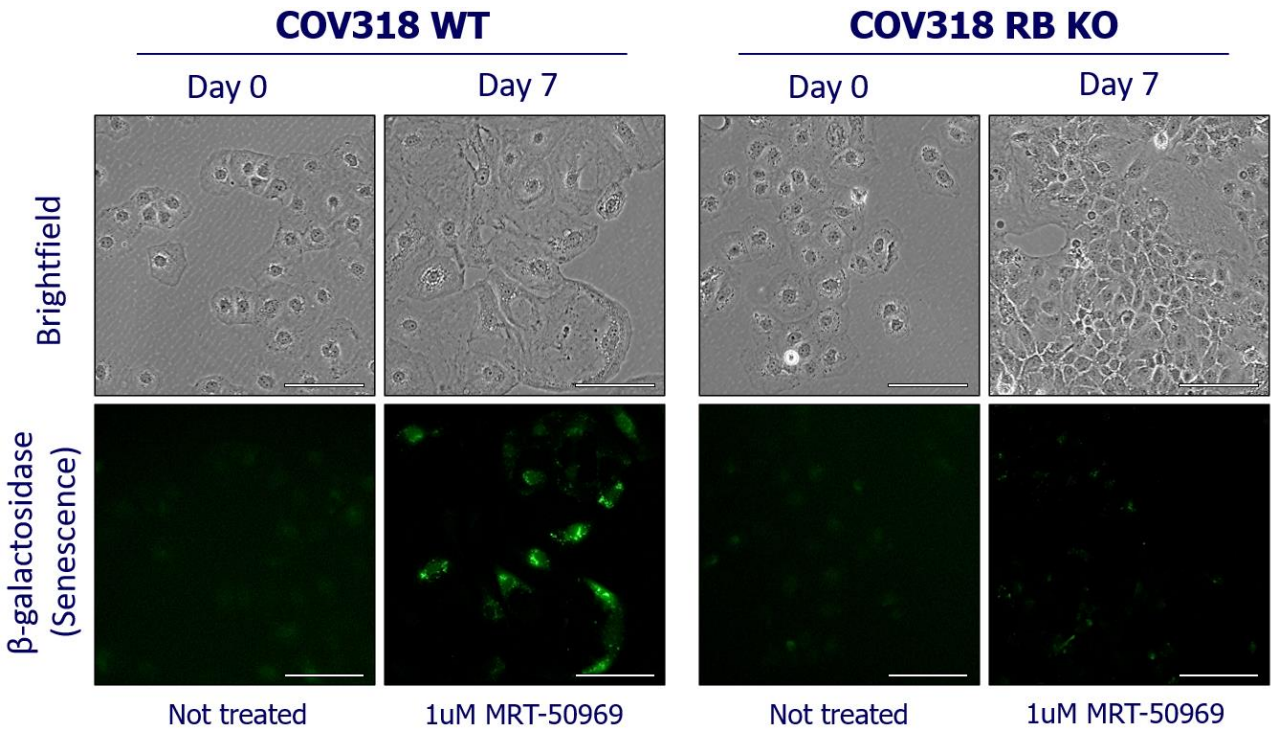
Cyclin E1 MGD-Induced Growth Suppression and Senescence Induction is Mediated by RB

Loss of RB blunts growth suppression induced by MRT-50969



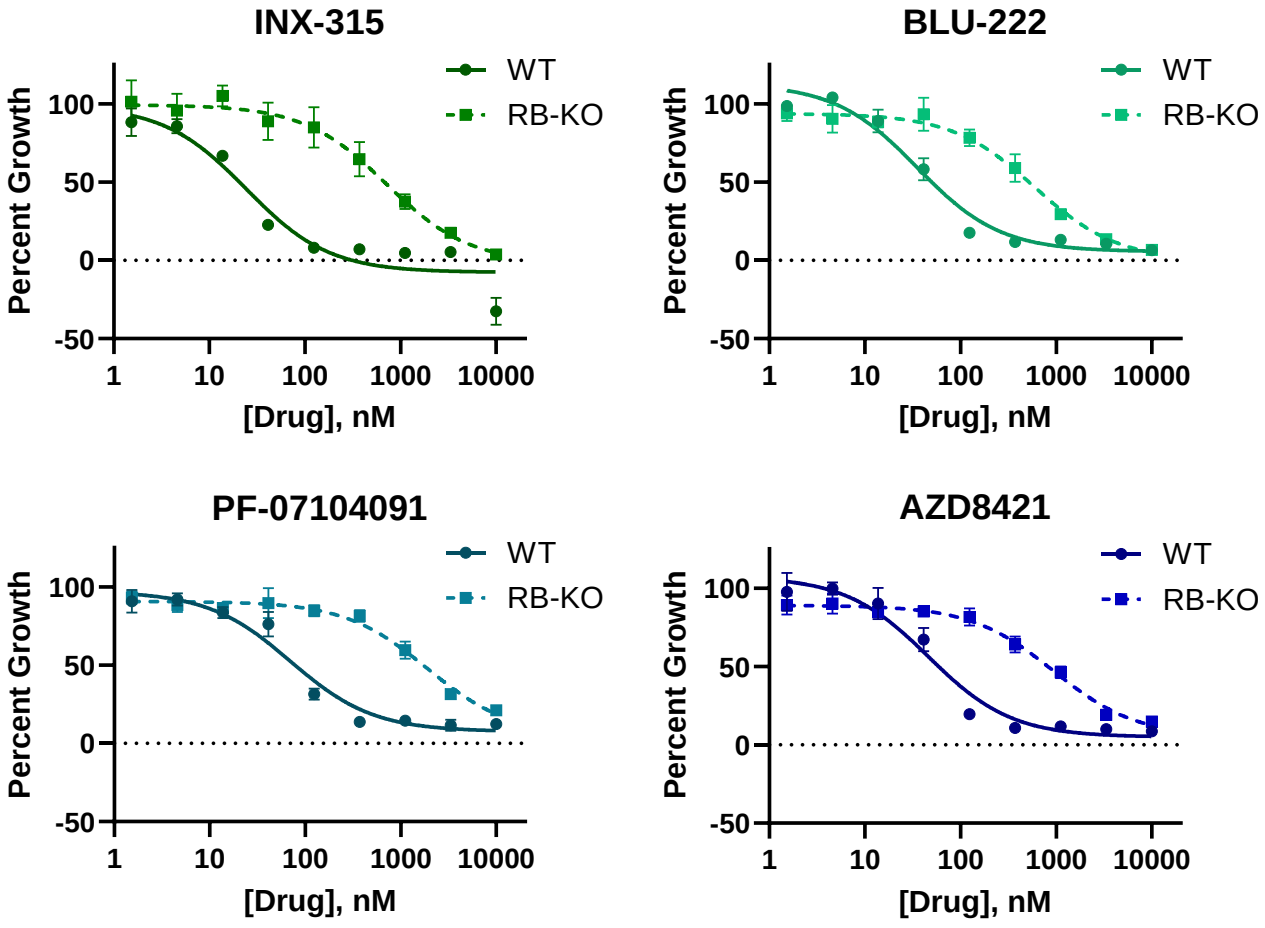
CyQuant, 5 days

Induction of senescence by cyclin E1 degradation is RB-dependent



Senescence visualized with CellEvent Senescence Green
Images: 10X; Scale-bar: 300µm

Cyclin E1 MGD is More Dependent on RB Signaling than Clinical Stage CDK2 inhibitors



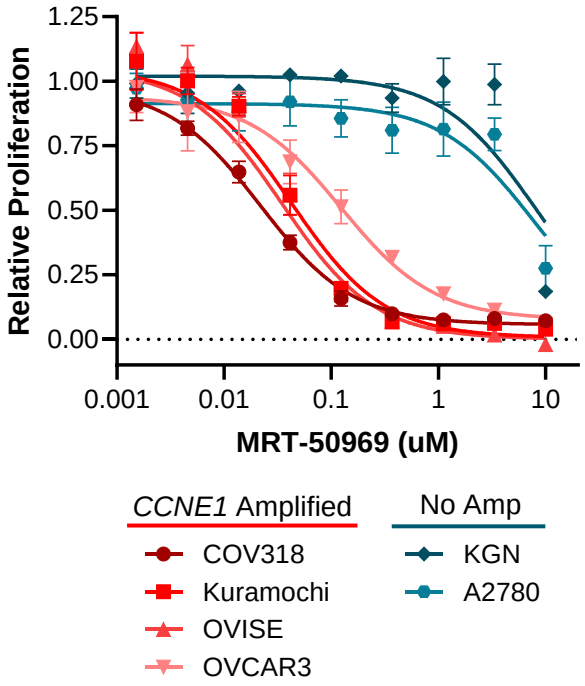
Compound	MKN1 GI_{50} (nM)	
	WT	RB-KO
MRT-50969	**4.8**	**4665**
INX-315	21	675
BLU-222	50	518
PF-07104091	78	1706
AZD8421	59	817

CDK2 inhibitors

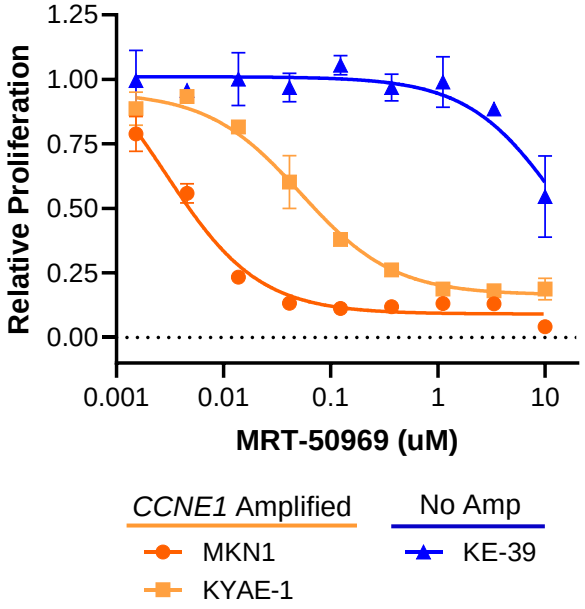
5 Day CyQuant Assay, MKN1 Cell Line +/- RB

MRT-50969 Exhibits Preferential Growth Suppression in *CCNE1* Amplified Cell Lines of Multiple Lineages

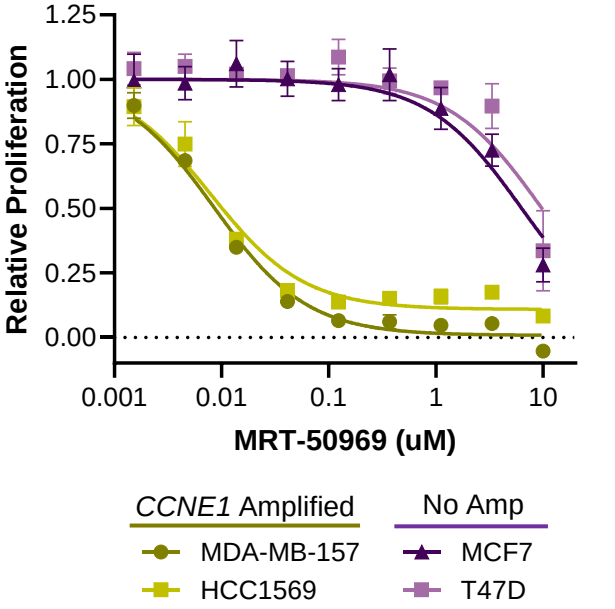
Ovarian cancer



Gastric cancer



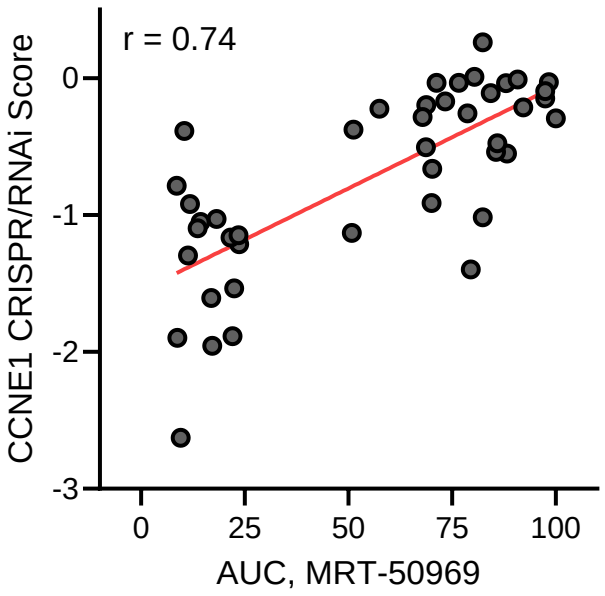
Breast cancer



CyQuant, 5 days

Cyclin E1 MGD Sensitivity is Highly Correlated with *CCNE1* Gene Dependency, Copy Number and Expression

Gene dependency



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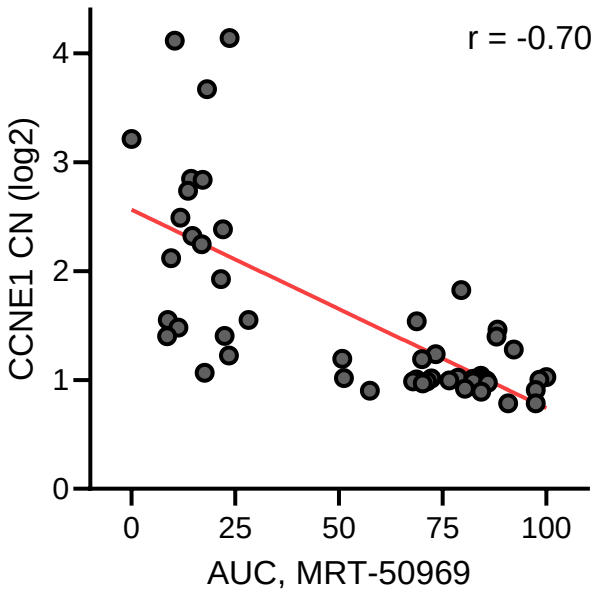
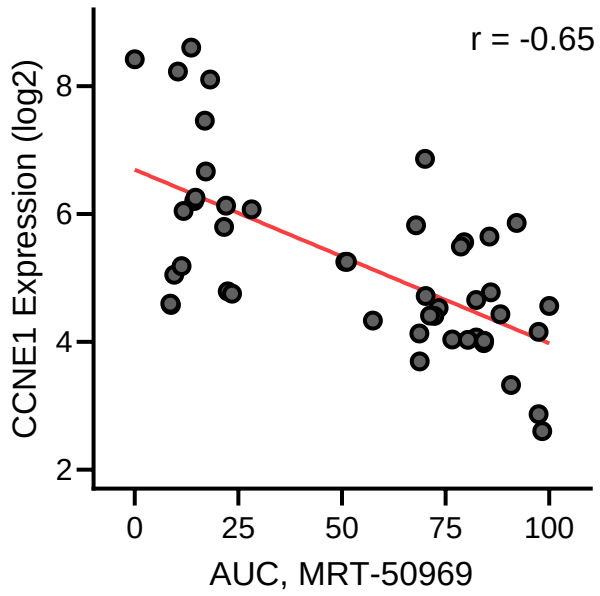
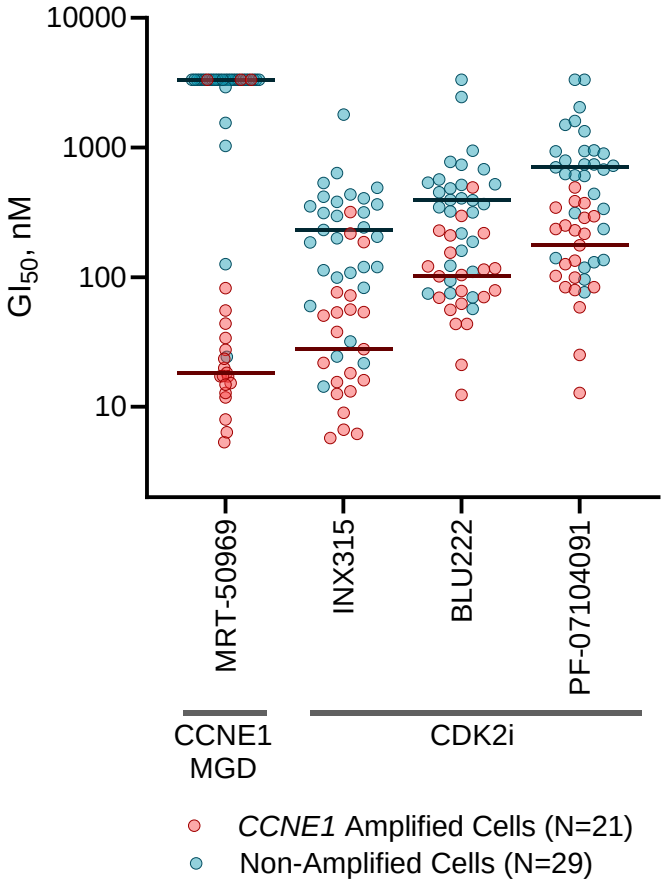


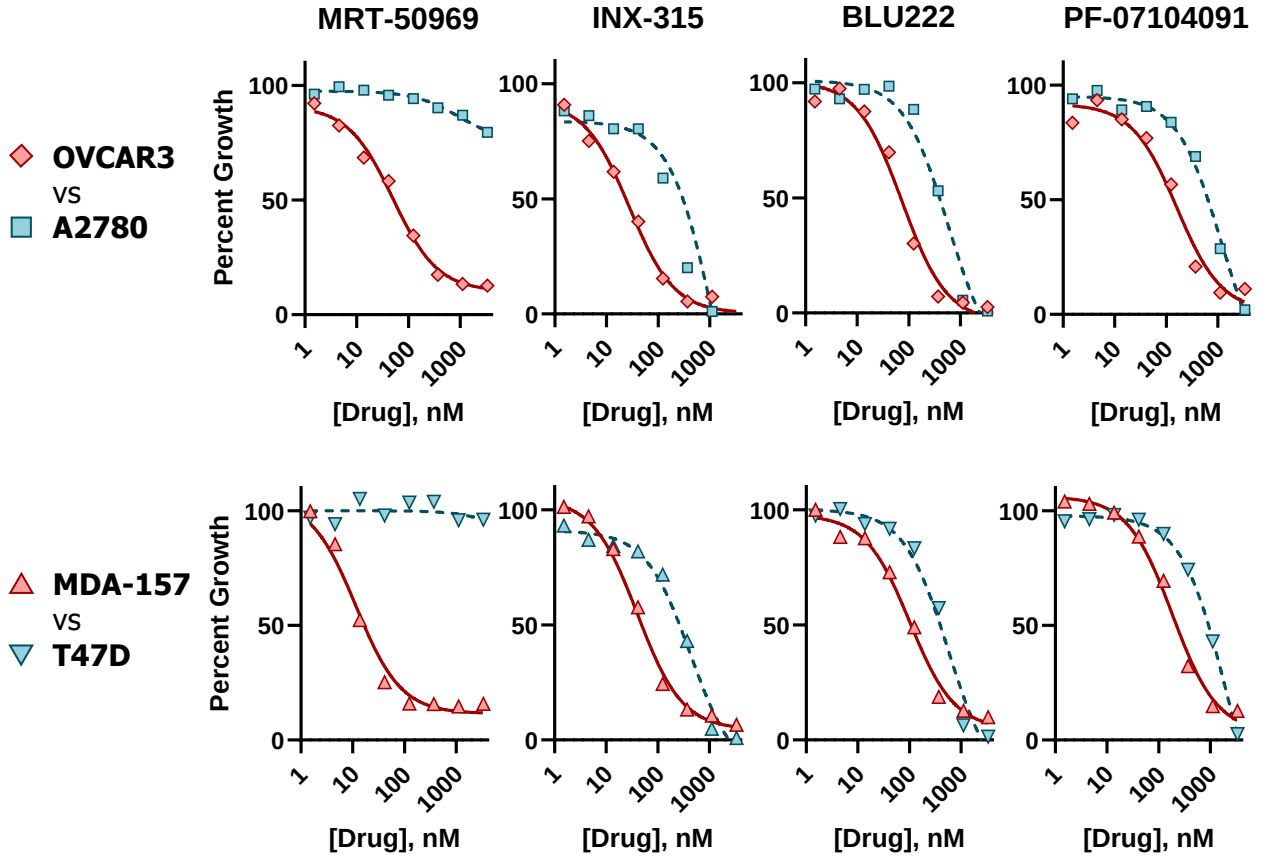
mRNA expression



5 Day CyQuant assay, 50 cancer cell line panel;
Gene dependency and genomics data from DepMap/Broad Institute

MRT-50969 Shows Superior Differential Activity in *CCNE1* Dependent Cell Lines Compared to Clinical-Stage CDK2 Inhibitors



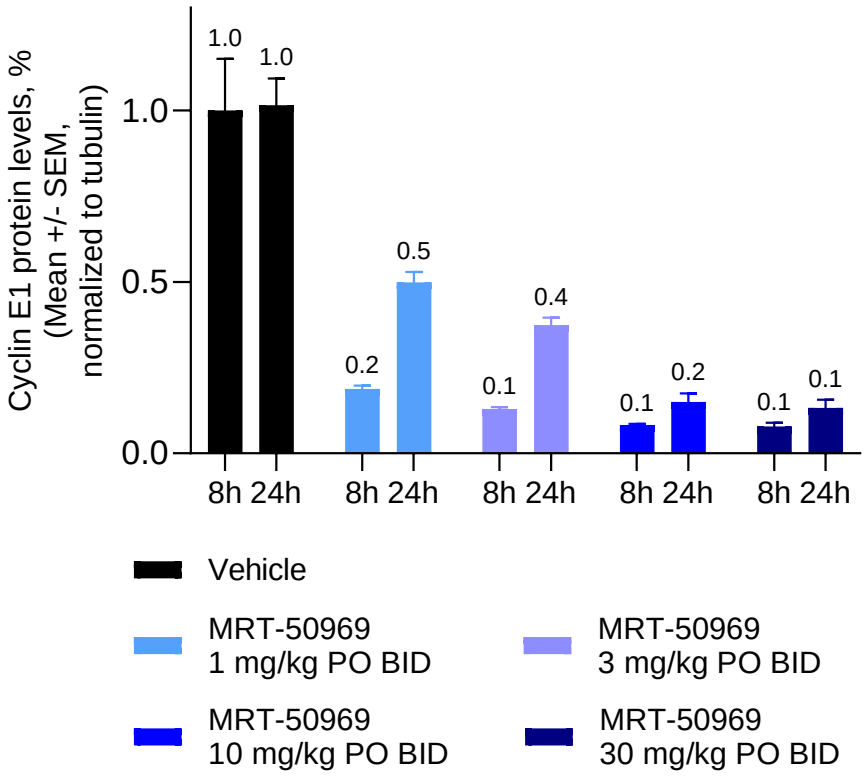


5 Day CyQuant assay, bars indicate median GI_{50}

GI_{50} = growth inhibition 50%, the concentration of drug required to inhibit the growth of cancer cells in vitro by 50%

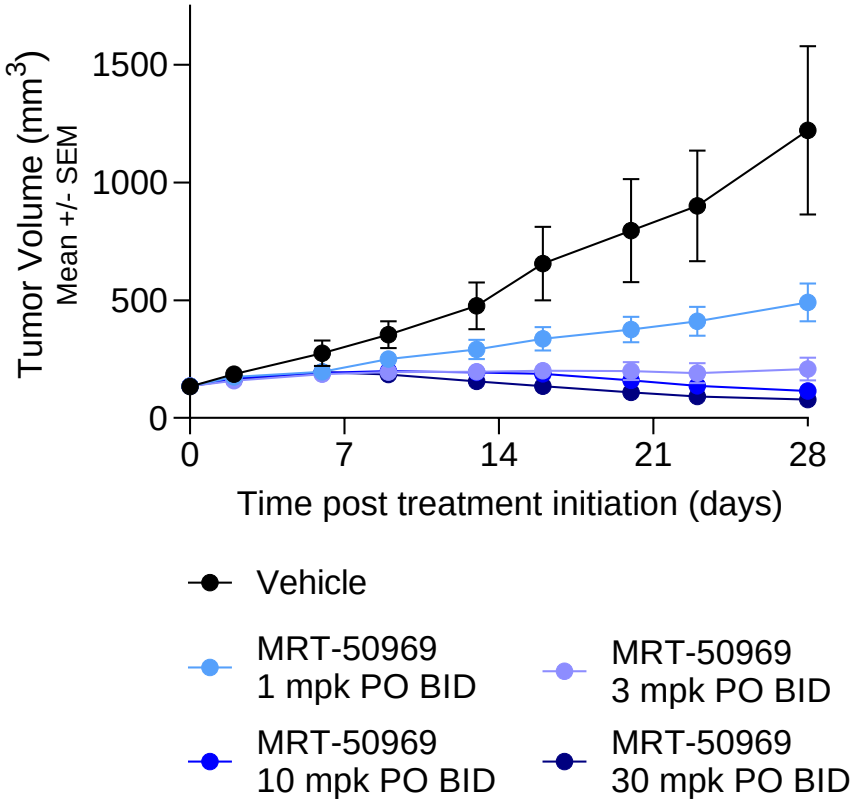
MRT-50969 Inhibits Tumor Growth in a *CCNE1* Amplified Breast Cancer Model *in vivo*

MRT-50969 degrades cyclin E1 *in vivo*



Day 28/8h and 24h PD, Western blot, HCC1569 CDX

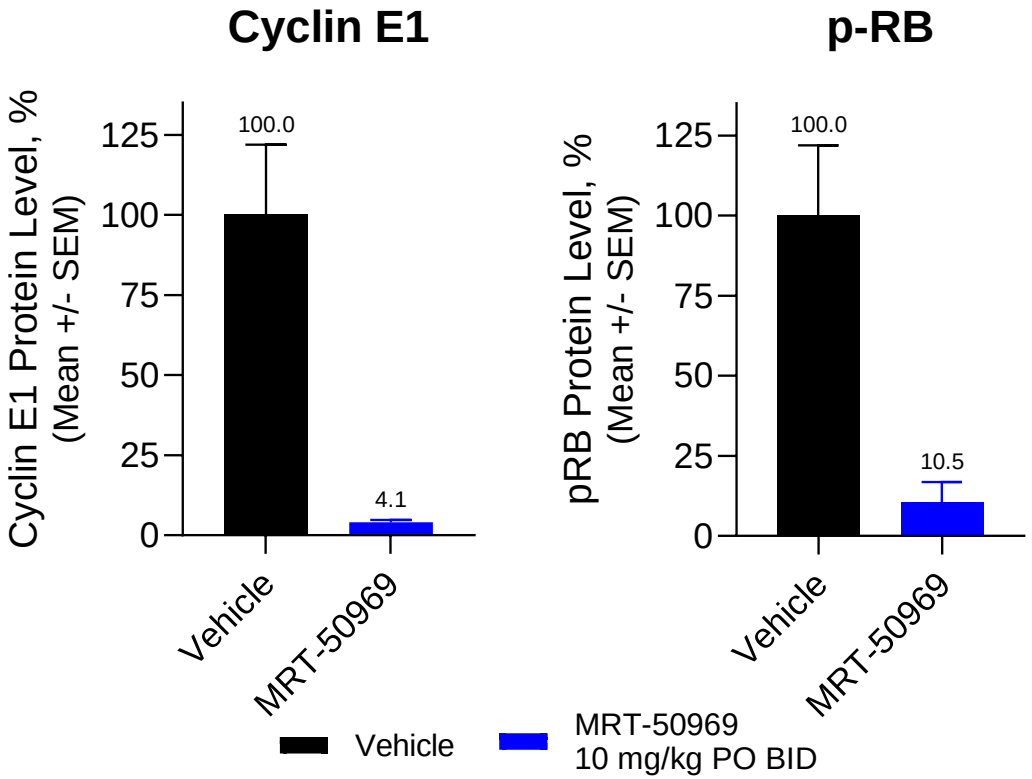
MRT-50969 inhibits tumor growth in *CCNE1* amplified breast cancer model



HCC1569 CDX, 28-day efficacy study

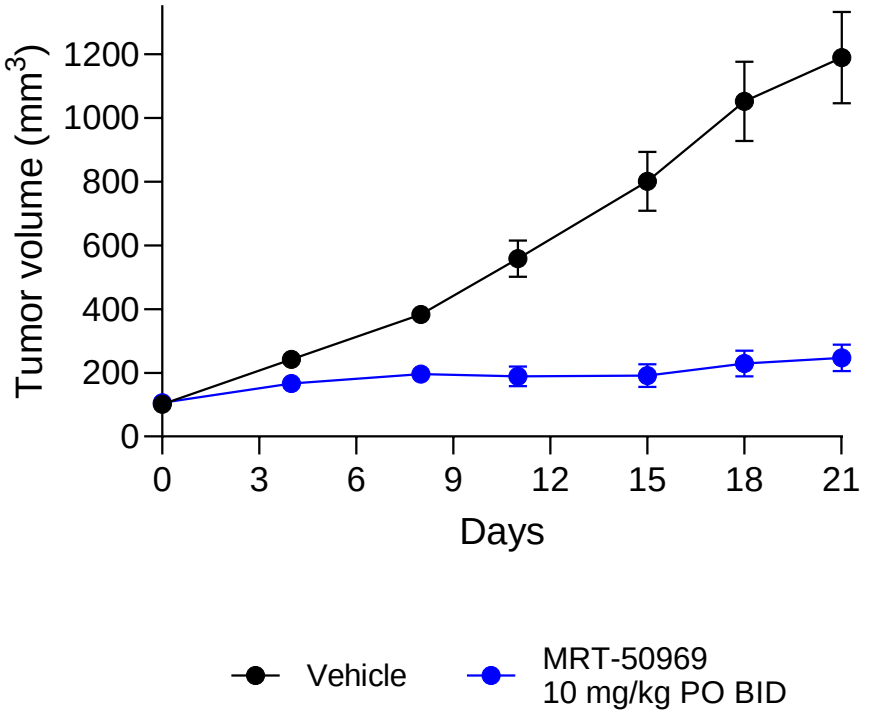
MRT-50969 Inhibits Tumor Growth in a *CCNE1* Amplified Gastric Cancer Model *in vivo*

MRT-50969 degrades cyclin E1 and inhibits downstream pathway activity *in vivo*



Day 21/8h PD, Western blot, MKN1 CDX
Protein level normalized to tubulin

MRT-50969 inhibits tumor growth in *CCNE1* amplified gastric cancer model



21-day efficacy study in MKN1 CDX model

Cyclin E1 Program

- First-in-class, **highly selective** cyclin E1-targeting molecular glue degraders; previously undruggable target
- Sensitivity to cyclin E1 MGD **parallels genetic dependency**, suggesting on-target MGD activity
- *CCNE1* amplified cell lines (ovarian, endometrial, gastric, breast) are sensitive to cyclin E1 degradation
- RB-dependent activity indicates on-target effects and **differentiates from clinical-stage CDK2 inhibitors**
- **Monotherapy efficacy** seen in *CCNE1*-amplified cancer models *in vivo*

Thank You to the Global Monte Rosa Team

Boston

Basel


Thank You
Monte Rosa
Therapeutics