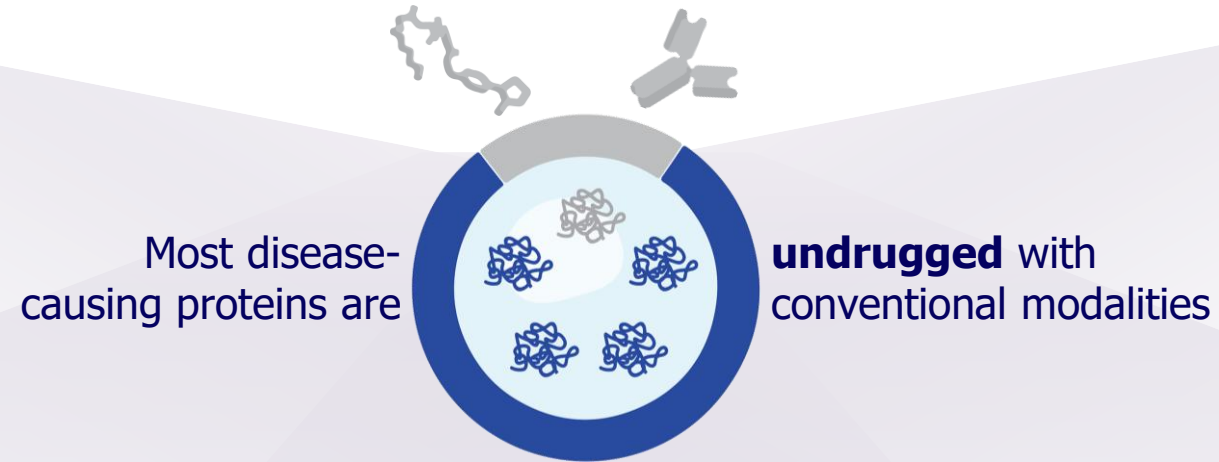


# Selective targeting of CCNE1 using molecular glue degraders for the treatment of *CCNE1* amplified cancers

Ralph Tiedt, Monte Rosa Therapeutics  
AACR Annual Meeting 2026



# Monte Rosa MGDs: Opportunity for Paradigm-Changing Medicines



## **MGDs**



**Clinically validated modality**



**Exquisite selectivity**



**Novel target space**



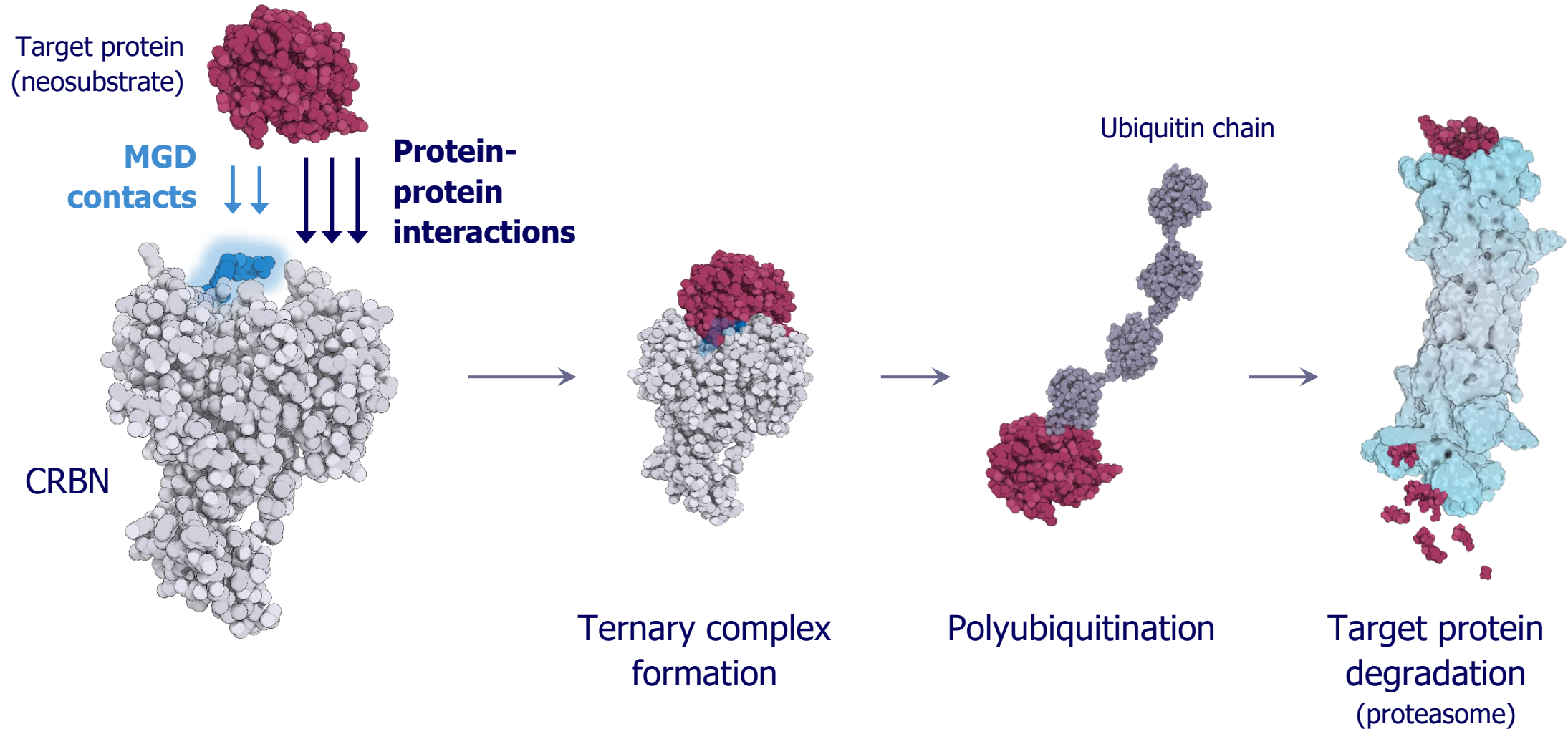
**Scalable manufacturing**



**Oral dosing**

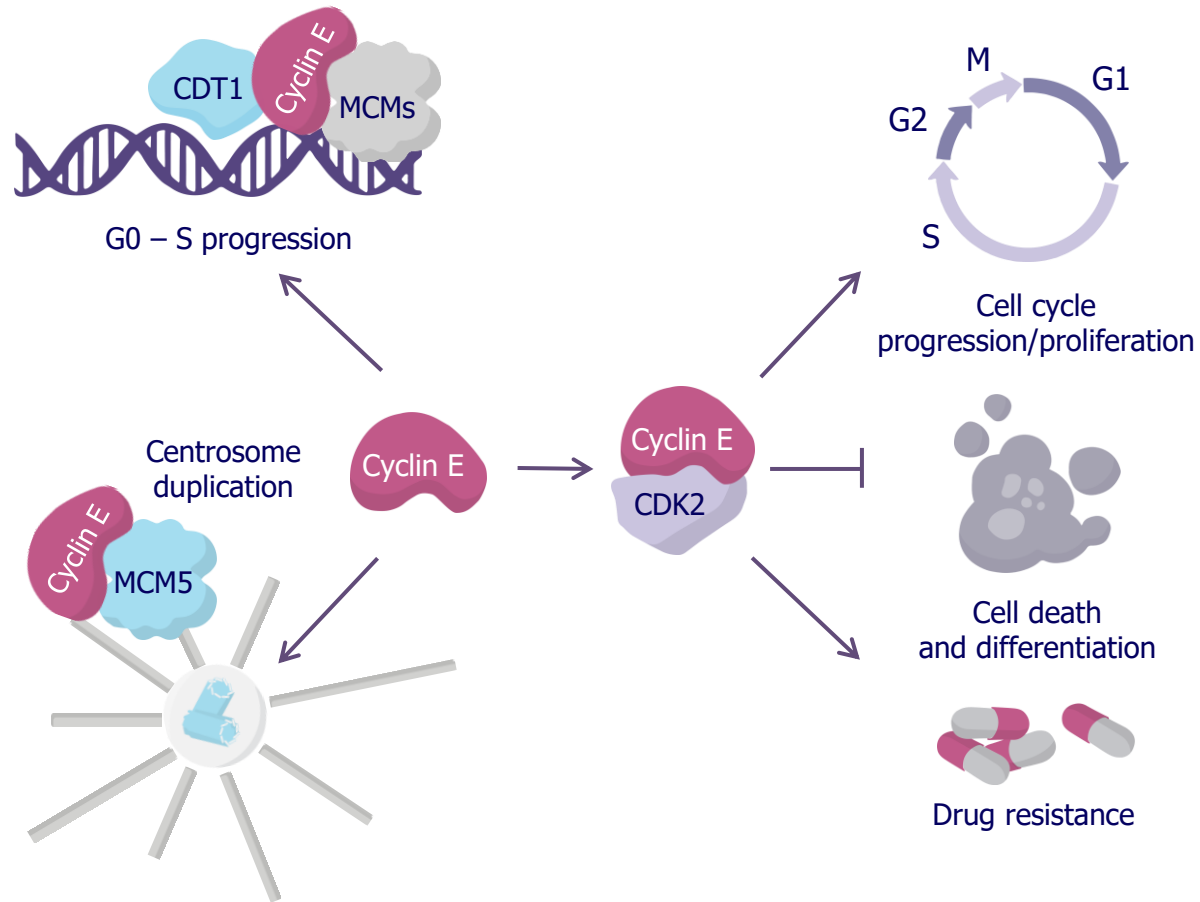
Like RNAi and CRISPR, Monte Rosa's **MGDs** have the potential to unlock **undruggable target space** but with the **advantages of oral small molecules**

# Molecular Glue Degradators (MGDs) Facilitate Targeted Protein Degradation Independent of Druggable Pockets on Target Proteins



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

## Cyclin E drives multiple hallmark cancer mechanisms



## Therapeutic hypothesis:

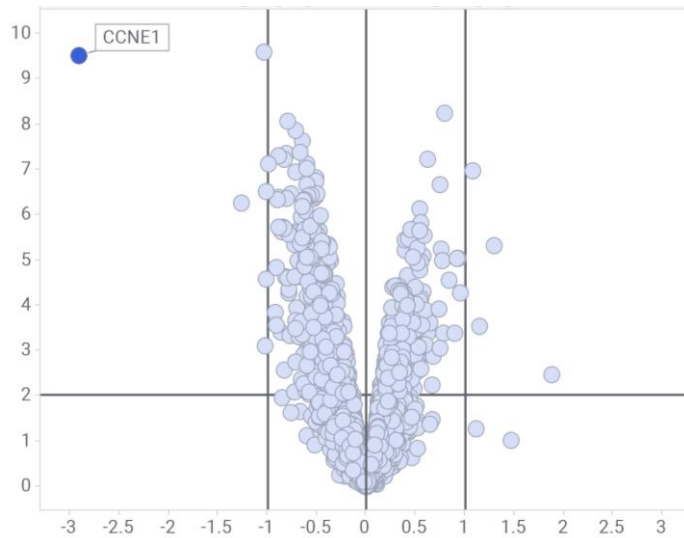
- CCNE1 (Cyclin E1) is a well-recognized human oncogene that drives multiple hallmarks of cancer, and has been considered undruggable
- Selective degradation of cyclin E1 can target tumors with deregulated cyclin E1 (amplification or overexpression)

## Clinical opportunity:

- First-in-class Cyclin E1 degraders for *CCNE1* amplified cancers
  - Ovarian (~20% of ~80K patients), endometrial (~10% of ~50K patients), and gastroesophageal cancer (~10% of ~200K patients), breast cancer and others

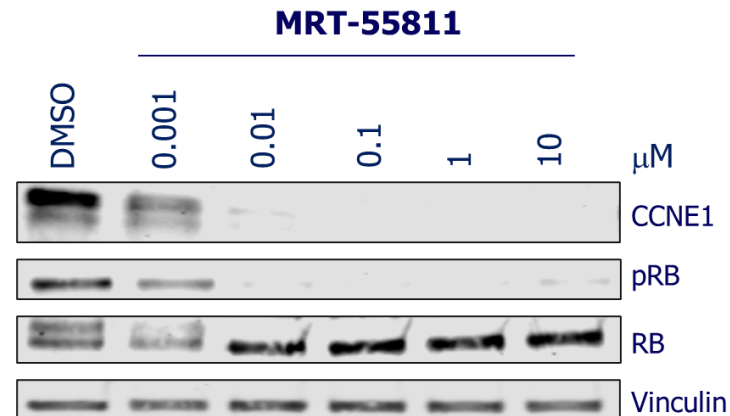
# MRT-55811 is a Potent and Highly Selective CCNE1-directed MGD

**MRT-55811 is highly selective for CCNE1**



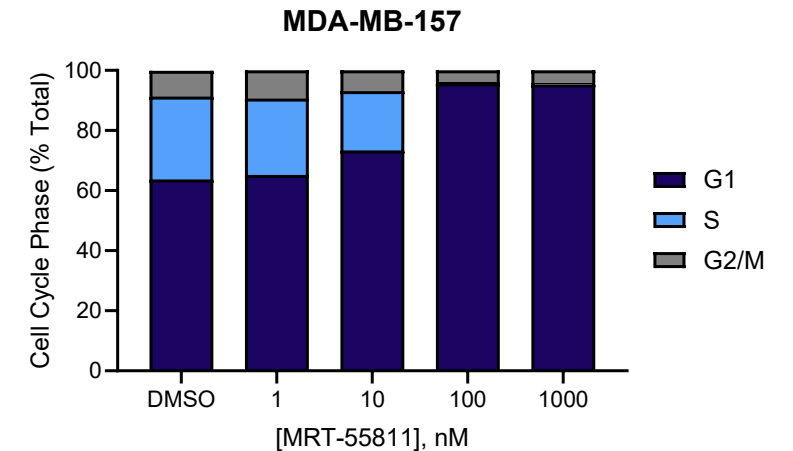
TMT Proteomics, MDA-MB-157 Rb K/O  
1 $\mu$ M, 24h

**CCNE1 degradation led to downstream pathway suppression**



Western blot, MDA-MB-157, 24h

**CCNE1 degradation induced robust cell cycle arrest**

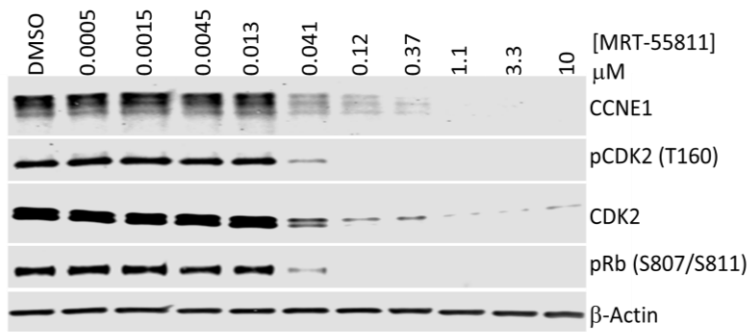


Flow Cytometry, EdU incorporation, 48h



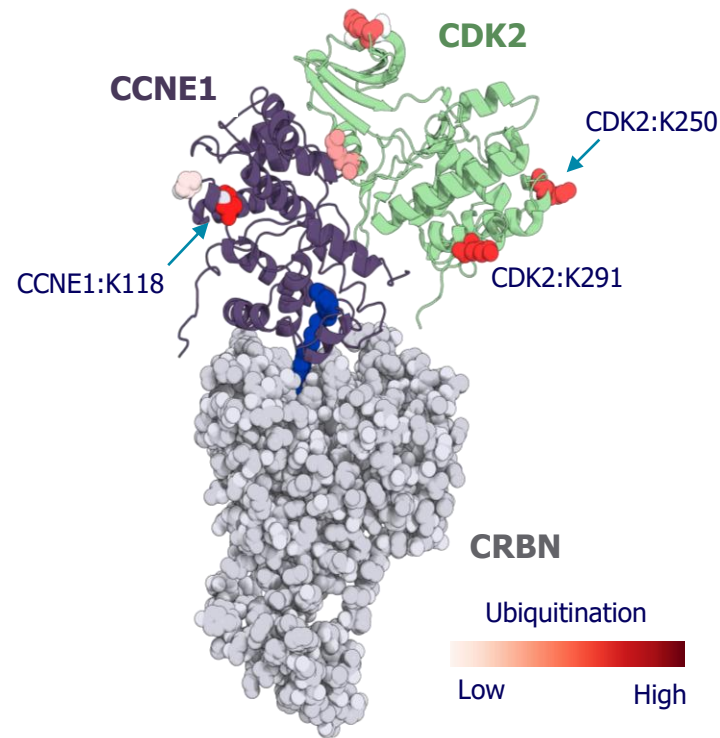
# MRT-55811 Induced CCNE1-CDK2 Holoenzyme Degradation in CCNE1 Amplified Cell Lines

## MRT-55811 induced co-degradation of CCNE1 and CDK2



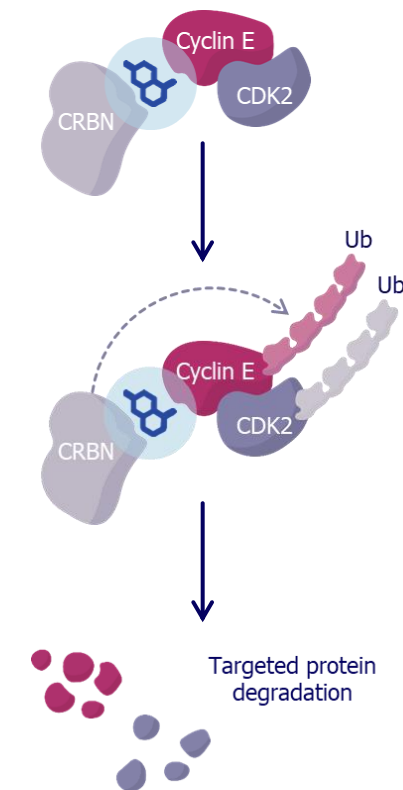
HCC1569, 24h treatment

## MRT-55811 induces CCNE1-CDK2 holoenzyme ubiquitination

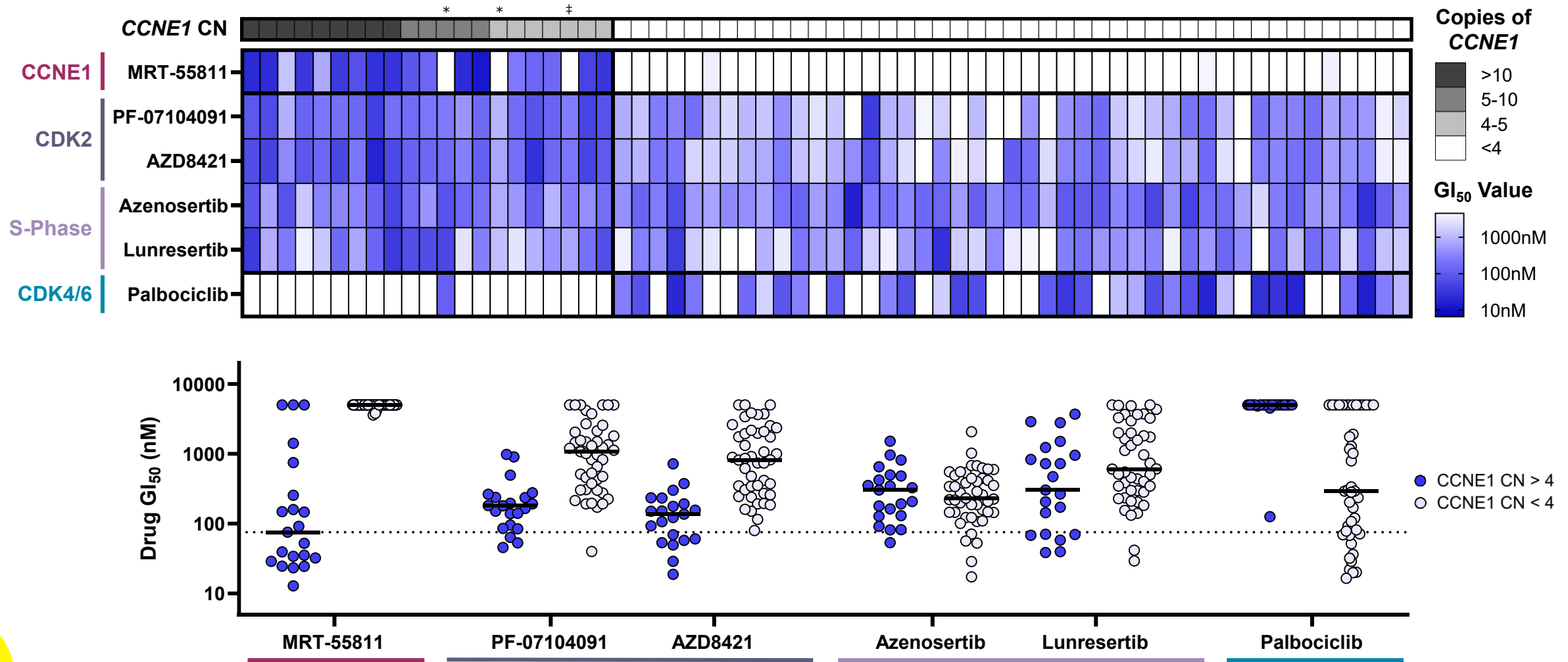


HCC1569, 1 $\mu$ M, 30 min treatment

## MRT-55811 induces CCNE1-CDK2 holoenzyme degradation



# CCNE1 MGD Exhibited Superior Selectivity for Cancers with High *CCNE1*



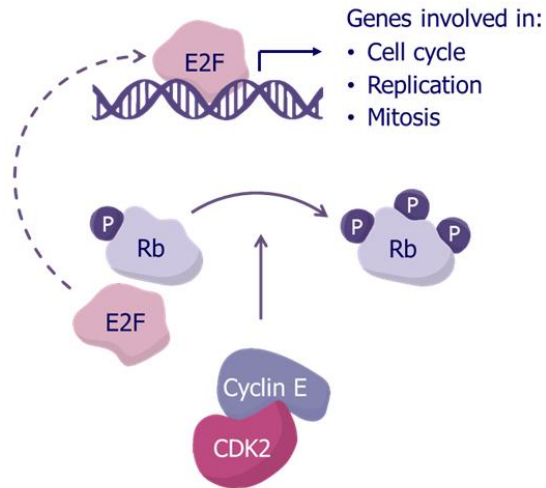
5-day CyQuant viability; ovarian, endometrial, gastric, and breast lineages (n=68)  
Rank-ordered by *CCNE1* copy number

\* Loss of p16 protein  
‡ Loss of RB protein

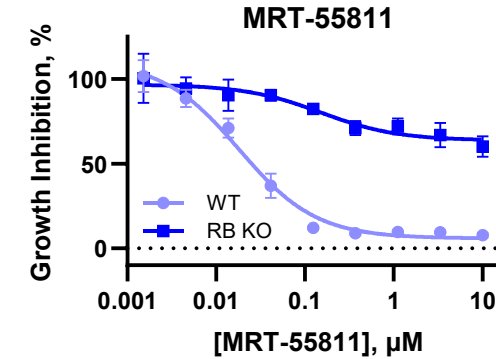
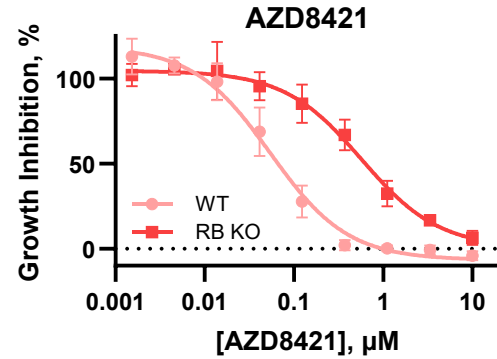


# MRT-55811 Induced Growth Suppression is RB-dependent

## CCNE1:CDK2 complex inactivates RB



## Growth suppression induced by MRT-55811, but not by CDK2i, is RB dependent



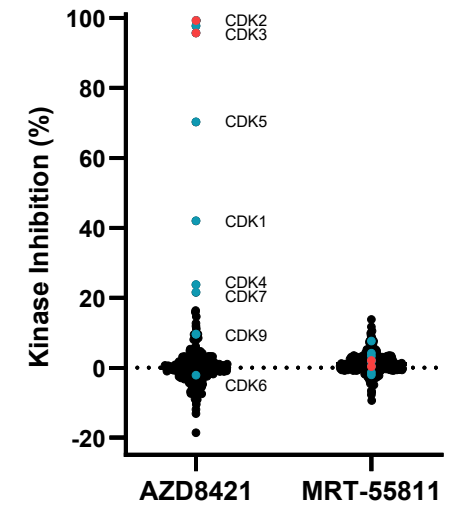
### MDA-MB-157

### MDA-MB-157 RB-KO



MDA-MB-157 (*CCNE1* amplified breast)  
 CyQuant assay – 5 day; Western blot – 24 hour treatment

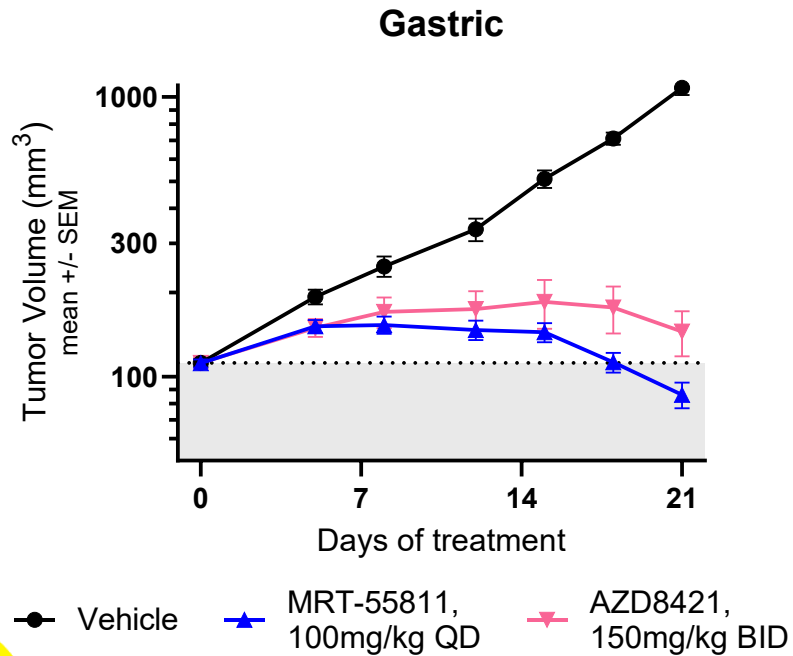
## CDK2i exhibit off-target activity of the CDK family



Kinase mobility shift assay  
 [Drug] =  $1\mu\text{M}$

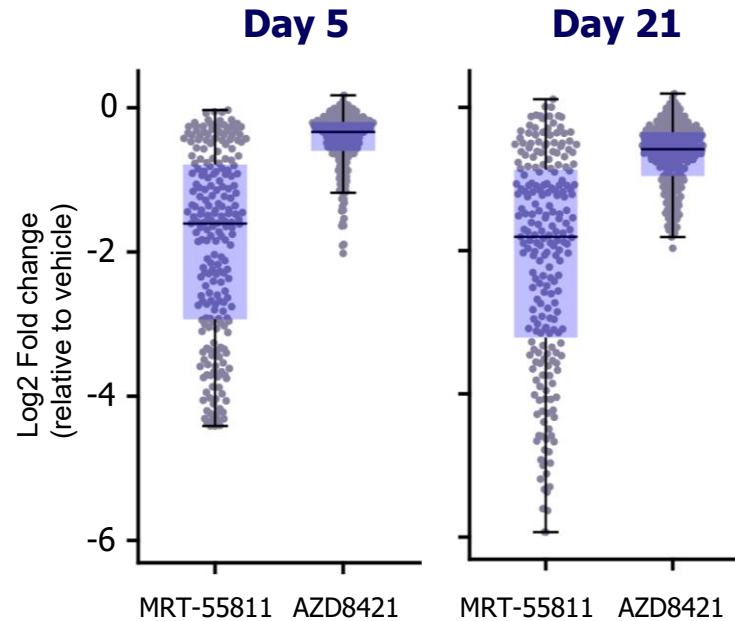
# MRT-55811 Treatment Resulted in Tumor Regression and Pathway Suppression in a *CCNE1* Amplified Gastric Model

**MRT-55811 induced tumor regression in *CCNE1* amplified gastric model**



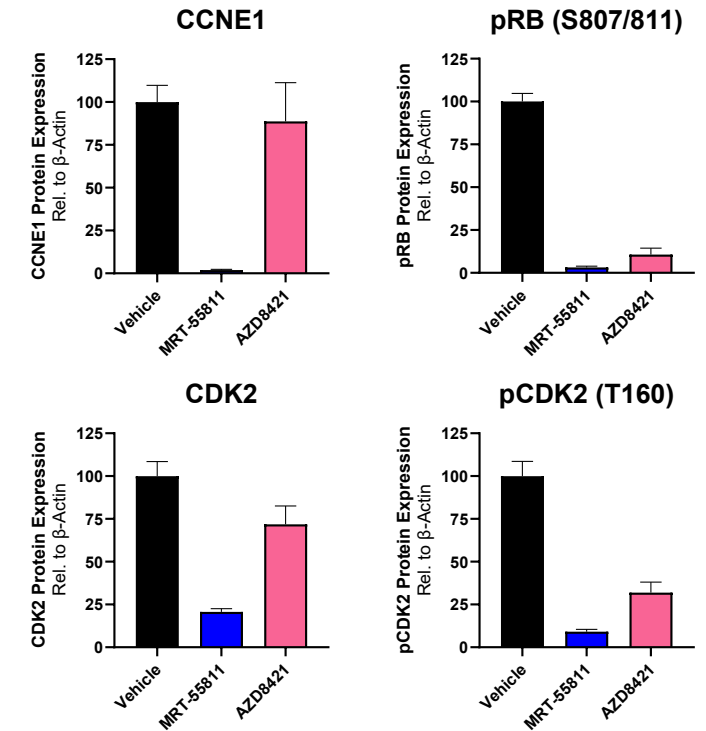
21-day efficacy study in MKN1 CDX

**MRT-55811 induced E2F signature suppression in tumors**



RNASeq  
Tumors collected 8h post first (MRT-55811) or 1h post second (AZD8421) daily dose

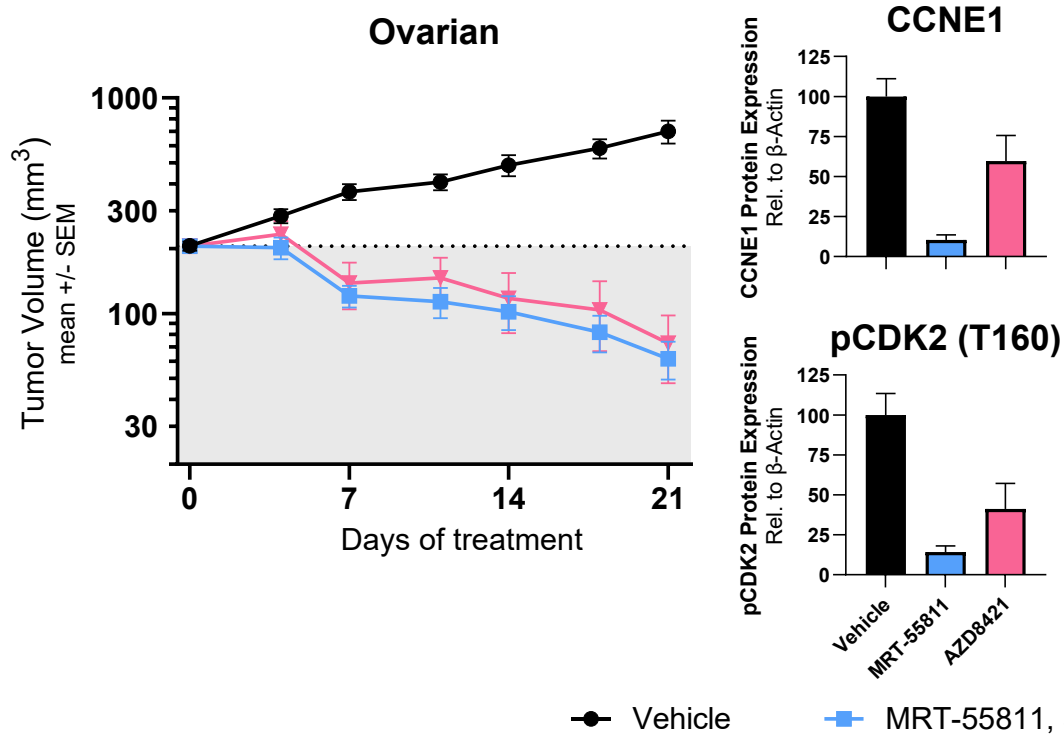
**MRT-55811 induced deep *CCNE1* degradation and pathway suppression**



Western blot, day 21  
Tumors collected 8h post first (MRT-55811) or 1h post second (AZD8421) daily dose

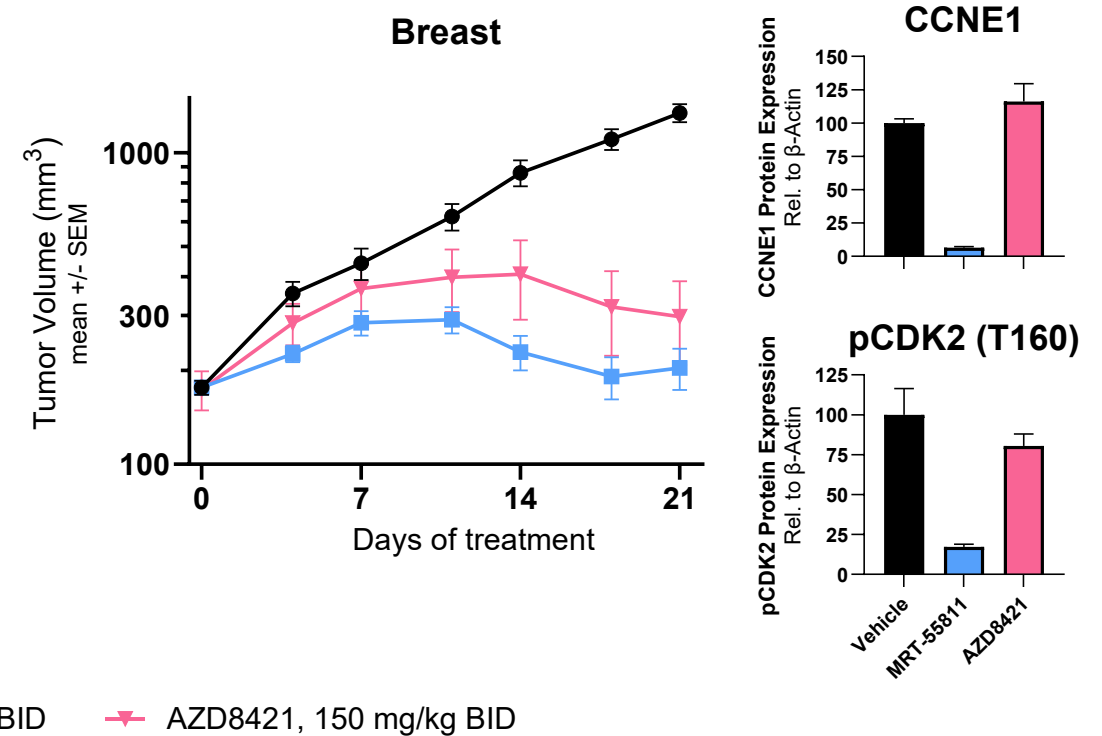
# MRT-55811 Treatment Resulted in Tumor Regression in Multiple *CCNE1* Amplified Models

## MRT-55811 induced tumor regression in *CCNE1* amplified ovarian model



21-day efficacy study in OVSAHO CDX

## MRT-55811 induced tumor regression in *CCNE1* amplified breast model



21-day efficacy study in HCC1569 CDX



## CCNE1 Program

- First-in-class, **highly selective** CCNE1-targeting molecular glue degrader; previously undruggable target
- *CCNE1* amplified cell lines (ovarian, endometrial, gastric, breast) are sensitive to CCNE1 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*, consistent with on-target downstream pathway suppression

