

ETX-197/BG-68501, a Potential Best-in-class Potent, Selective, Oral, Small Molecule CDK2 Inhibitor, has Anti-Tumor Activity in Cancer Models with Cyclin E Amplification or Deficiency in the Retinoblastoma 1 Gene.

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SUMMARY

In normal cells, there is redundancy in the role of the cell-cycle dependent kinases (CDKs) in regulating G1/S phase transition^{1,2}. In cancer cells, the regulation of G1/S transition can be subverted by (a) amplification and elevated expression of Cyclin E1 (CCNE1), or (b) mutation/loss of the Retinoblastoma 1 (RB1/RB) gene⁵⁻⁸. Cancer cells with these genomic alterations have been shown to exhibit profound sensitivity to CDK2 depletion, validating CDK2 as a potential therapeutic target.

- A broad range of aggressive cancers overexpress CCNE1 including gynecological (e.g., ovarian, endometrial), gastric, triple negative breast cancer (TNBC), and other cancers
- CCNE1 amplification correlates with poor survival (ovarian)
- Up-regulation of CCNE1 or loss of RB1 confers CDK4/6i- resistance in ER⁺HER2⁻ breast cancer
- CRISPR screening data from DepMap portal shows that cancer cells with CCNE1 amplification or RB1 mutation are highly sensitive to CDK2 depletion^{3,4}

Thus, selective targeting of CDK2 will inhibit cancer growth and may limit off-target CDK-driven toxicities. Here, we report the discovery and preclinical characterization of ETX-197, a potent and selective, orally bioavailable small molecule inhibitor of CDK2 activity.

BACKGROUND

Figure 1. Targeting Dysregulated CDK2 Activity in CCNE1 Amplified or RB1 Mutant Tumors

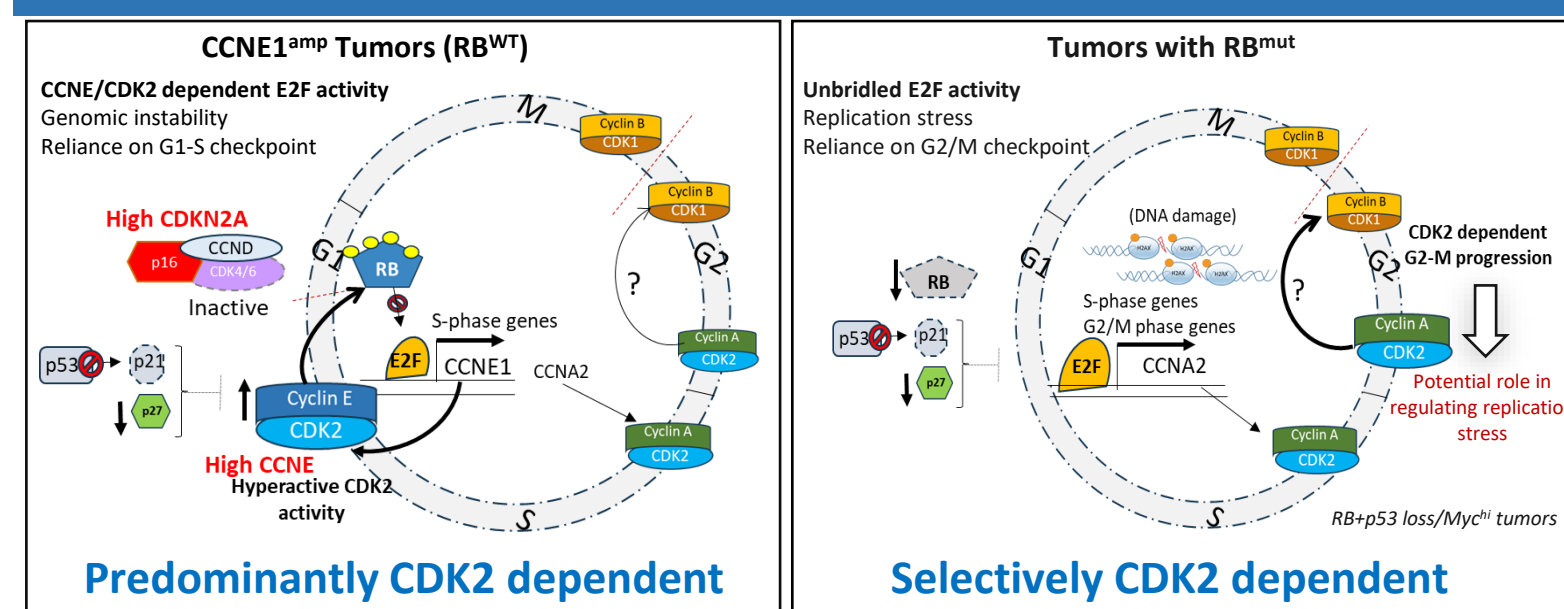


Figure 2. Functional Genomics Screens Confirm CCNE1 and RB1 Status as Predictors of Strong CDK2 Dependency in Cancer Cell Lines

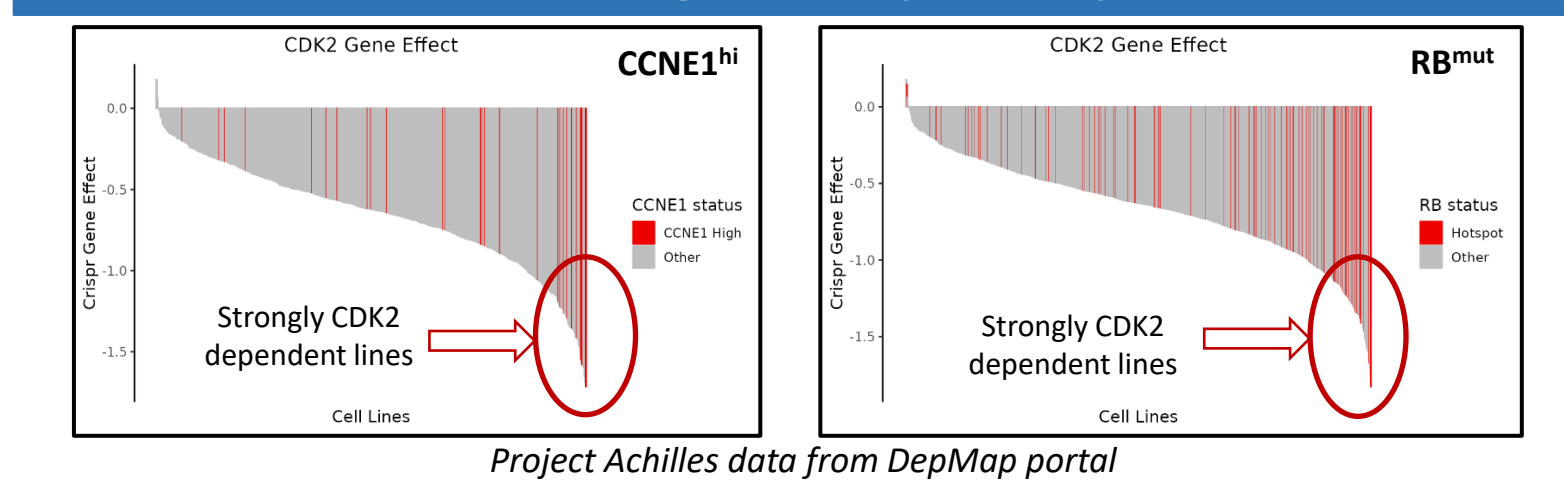


Figure 3. ETX-197 is a Potent and Selective, Orally Bioavailable Inhibitor of CDK2 Kinase Activity

ETX-197 shows improved potency and selectivity over PF07104091 in biochemical, biophysical and cellular assays

Kinome S(10) ^a	Biochemical activity ^b (IC ₅₀ ; nM)						
	CDK2:CycE1	CDK2:CycA2	CDK1:CycB1	CDK4:CycD1	CDK6:CycD3	CDK7:CycH	CDK9:CycT1
0.047	0.93	1.9	73.6	247.9	567.6	255.4	116.03

Compound	Biophysical (SPR)			Biochemical K _i		Cellular activity (IC ₅₀ ; nM)	
	k _{on} (M ⁻¹ s ⁻¹)	k _{off} (s ⁻¹)	K _D (nM)	K _i (nM)	OVCAR3 (pRB-S780; nM) ^c	TOV21G (pNPM1-T199; nM) ^d	Selectivity
ETX-197	1.48E+07	1.06E-03	7.18E-02	0.11	3	100	33 x
PF-07104091	1.43E+07	6.30E-03	4.42E-01	1.45	40	450	11 x

^aKinome S(10): Kinase hits with 90% efficiency as that of control at 2 μM. Competition binding assays @ KinomeScan with 403 non-mutant kinases
^bEnzyme activities IC₅₀ were measured at varying concentration of ATP using canonical CDK/Cyclin pairs as indicated
^cPhosphorylated RB1 (pRB-S780) protein was assessed by western blot in synchronized OVCA3 cells to reflect CDK2 cellular potency
^dp-NPM1(T199) is a measure of CDK1 activity in Nocodazole arrested TOV21G cells

Figure 4. ETX-197 Shows Selectivity for CCNE1^{amp} Cancer Cells and Growth Inhibition Correlates with CDK2 Dependence

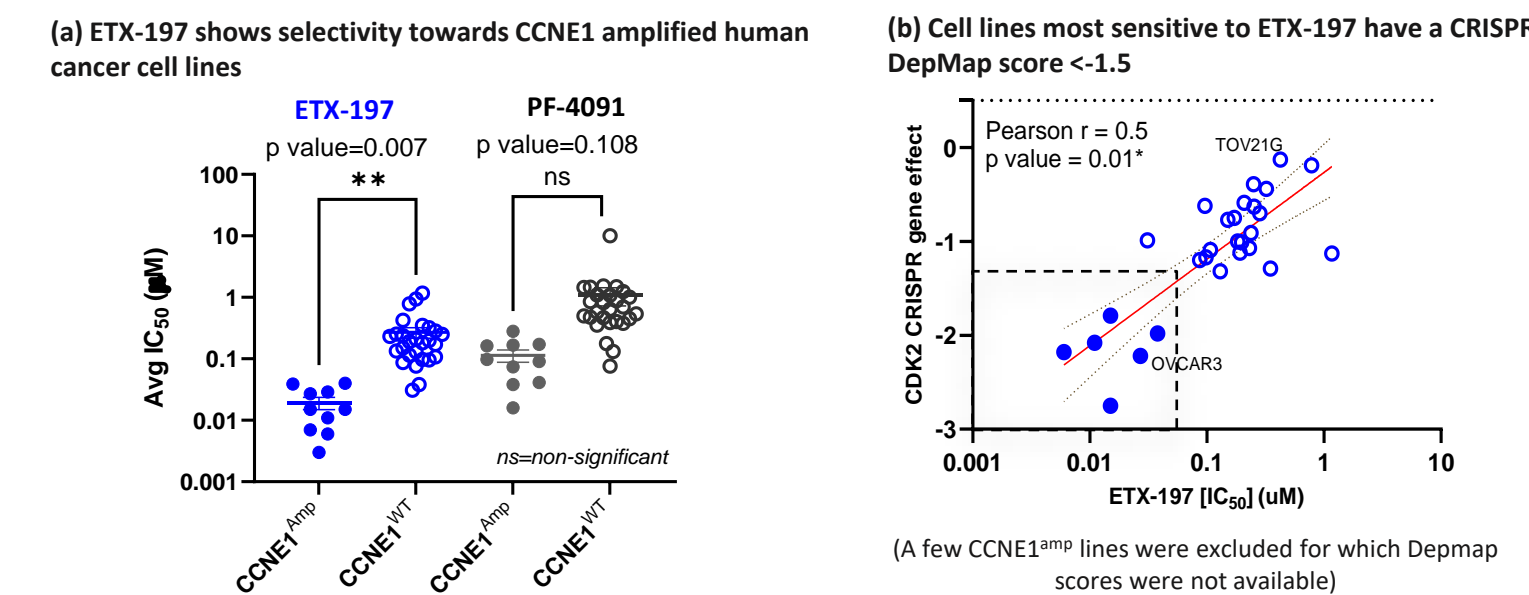
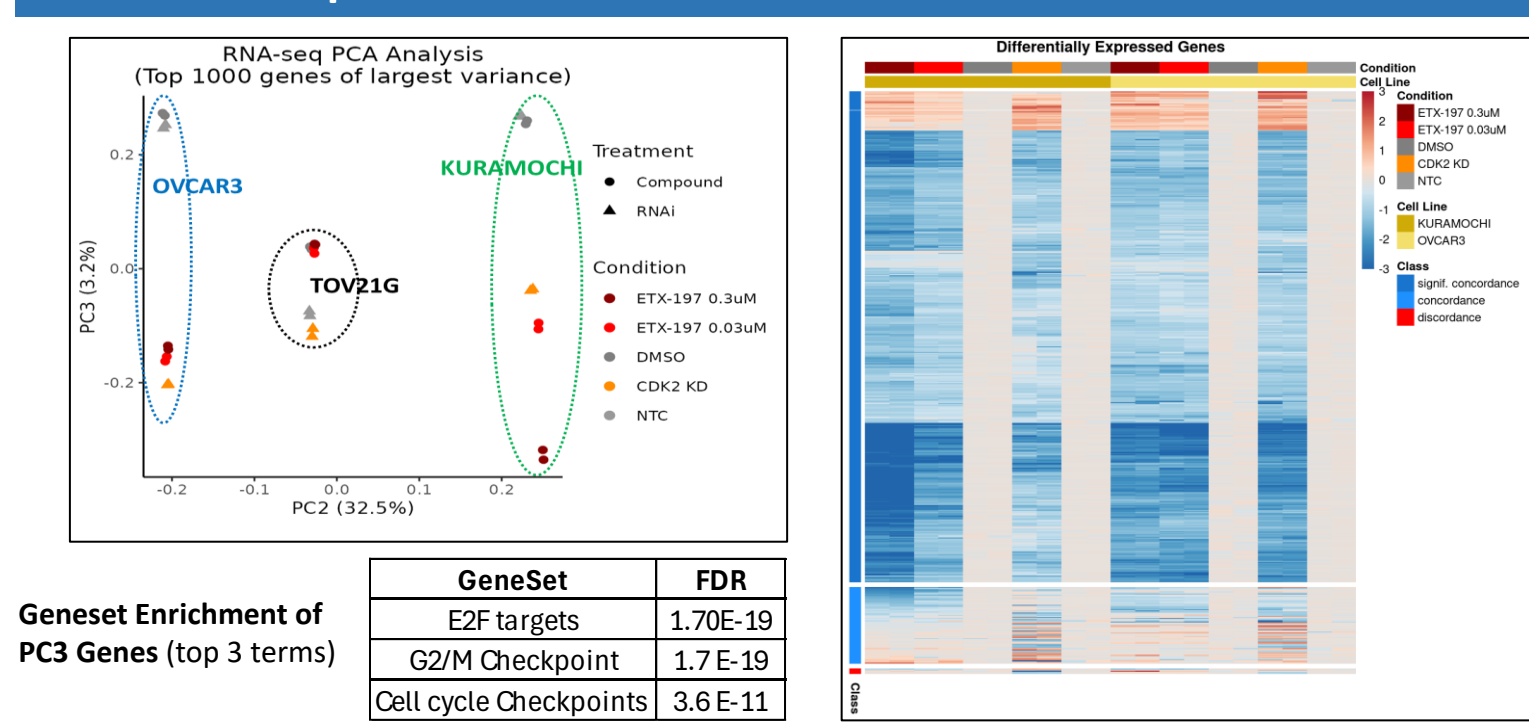


Figure 5. Bulk RNA-Seq Data Confirm ETX-197 Downregulated Genes Recapitulate CDK2 KD Profile in CDK2i Sensitive Cells



RESULTS

Figure 6. ETX-197 is Efficacious *In Vivo* and Demonstrates Dose-Dependent PD Response

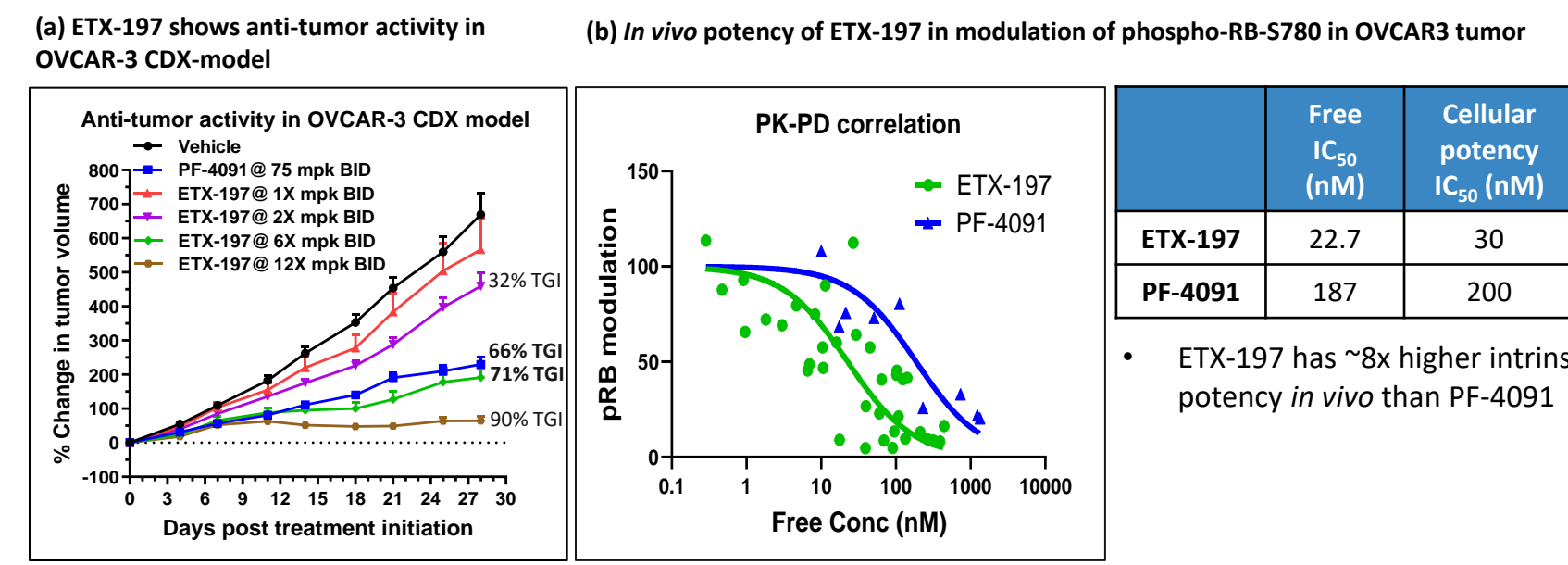


Figure 7. ETX-197 is Efficacious in CCNE^{hi} TNBC PDX models

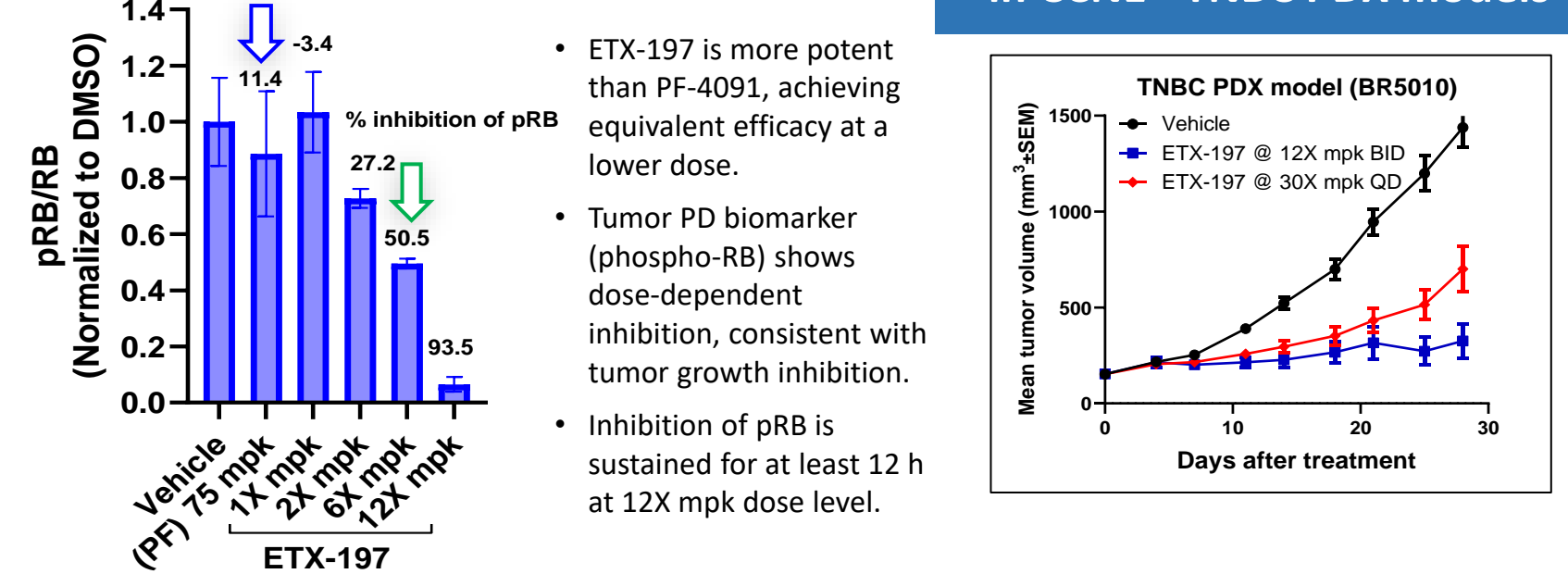


Figure 8. ETX-197 Shows Anti-Tumor Activity in Palbociclib-Resistant MCF-7 CDX model

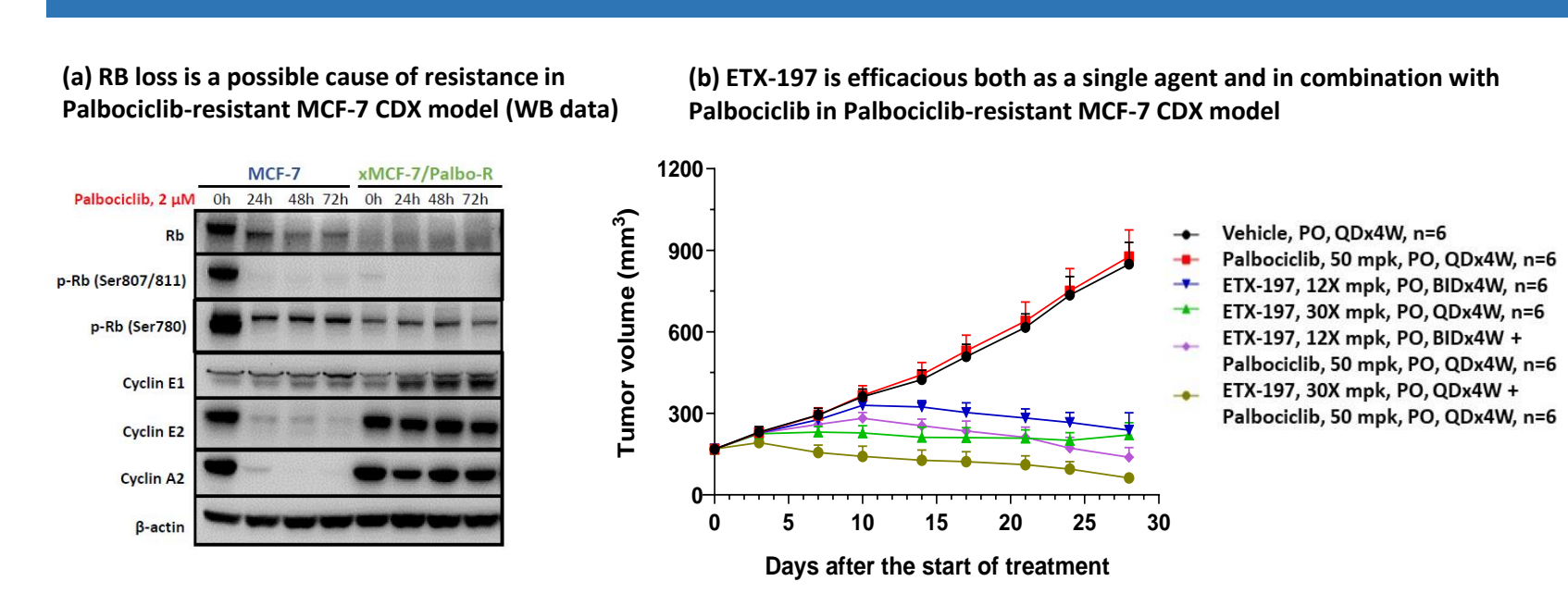


Figure 9. ETX-197 Treatment Correlates with Induction of G2/M Cell-cycle Arrest, DNA Damage and Apoptosis in CDK2i Sensitive RB^{mut} SCLC

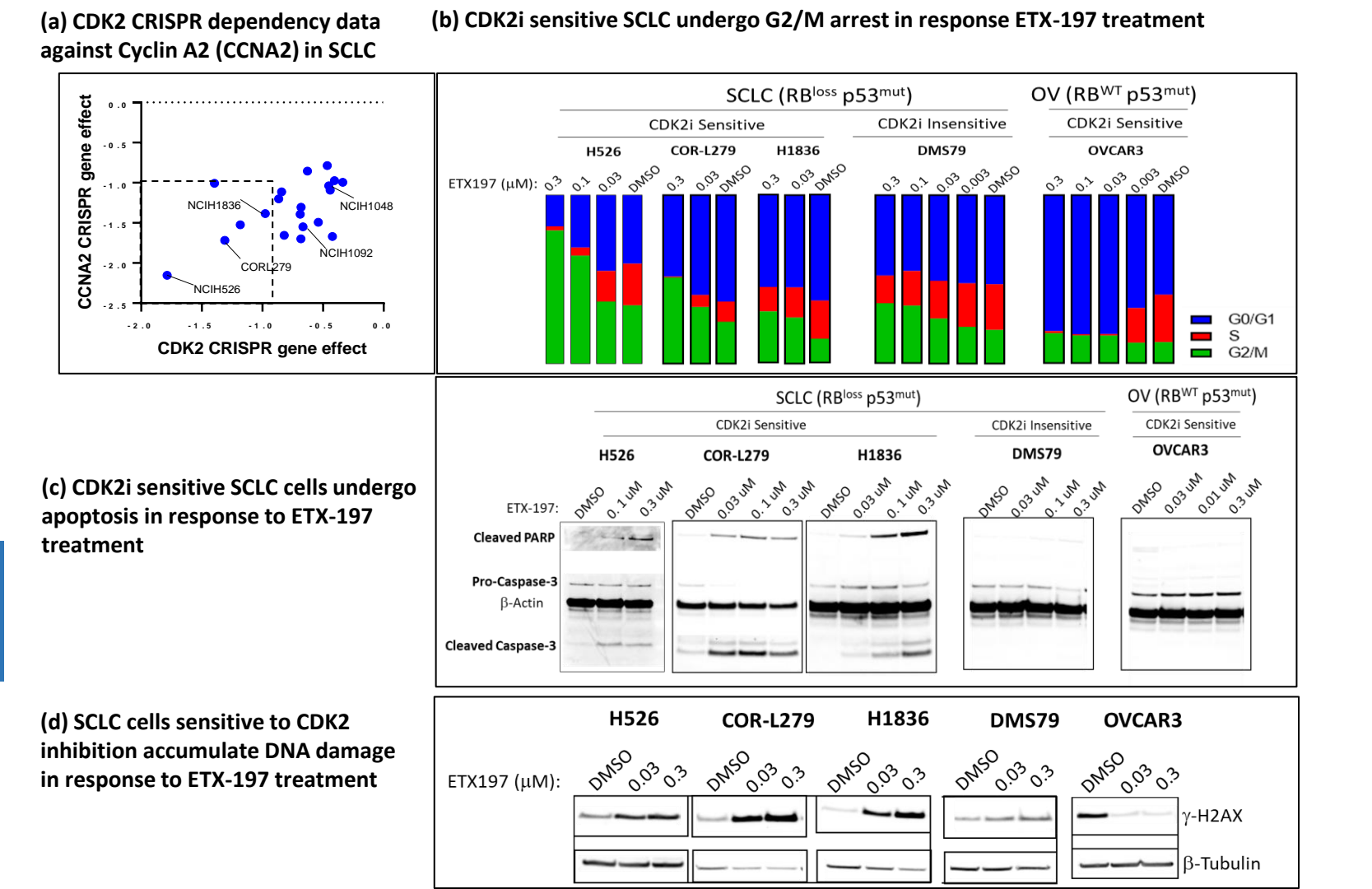
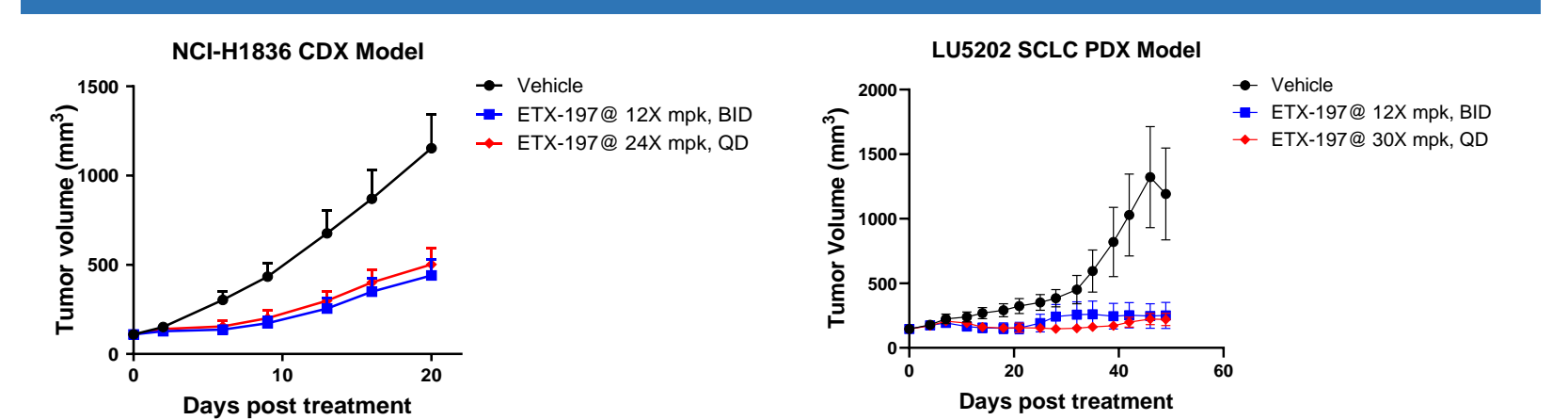


Figure 10. ETX-197 Shows Anti-tumor Activity in RB^{mut} SCLC CDX and PDX models



CONCLUSION

- ETX-197 is a selective and potent, oral, small molecule CDK2 inhibitor
- ETX-197 demonstrates single agent anti-tumor efficacy in both RB^{WT} CCNE1-amplified and RB1 deficient CDX and PDX mouse models
- ETX-197 shows anti-tumor activity in a breast cancer xenograft model with acquired resistance to a CDK4/6 inhibitor due to loss of RB1 expression.
- ETX-197 is being clinically developed by BeiGene as BG-68501, in a first-in-human, Phase 1a/1b in patients with advanced, nonresectable, or metastatic solid tumors (NCT06257264; Poster # P4-08-20)

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