CDK4/6-related *in vivo* models

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2021.03

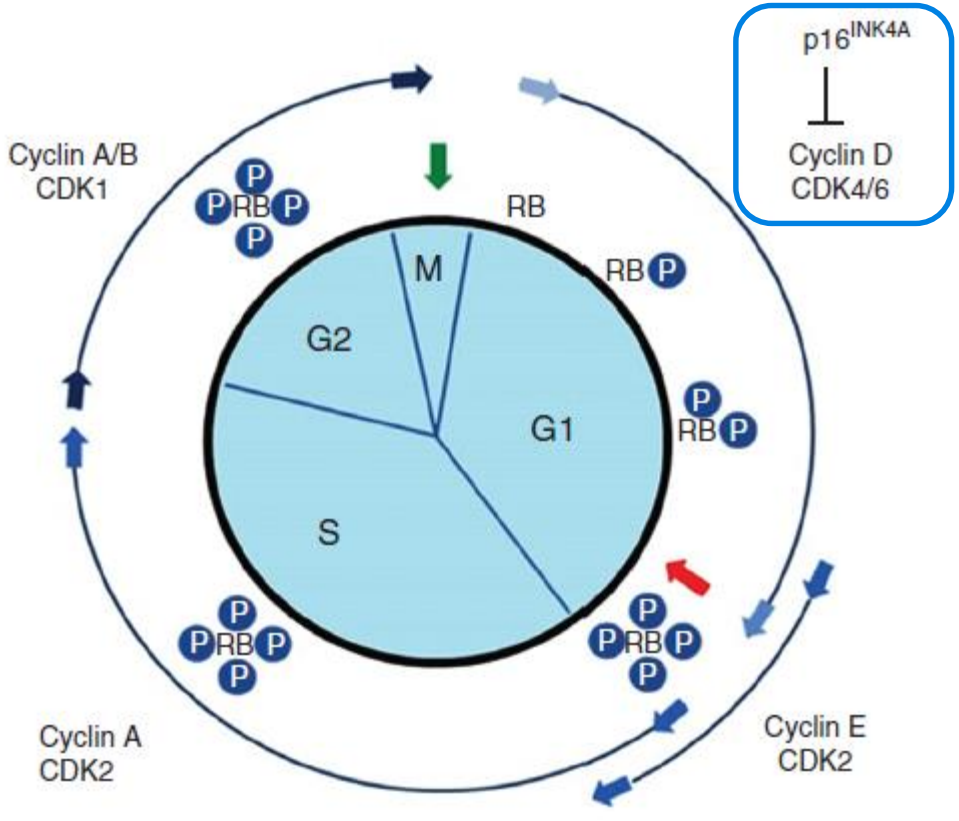
Outline

- **CDK4/6 background as a drug target**
  - CDK4/6 biology
  - CDK4/6 inhibitors
- **CDK4/6-related CDX models**
  - CDK4/6-related CDX model summary
  - Model characterization and SOC data
- **CDK4/6-related PDX models**
  - CDK4/6-related PDX model summary and SOC data

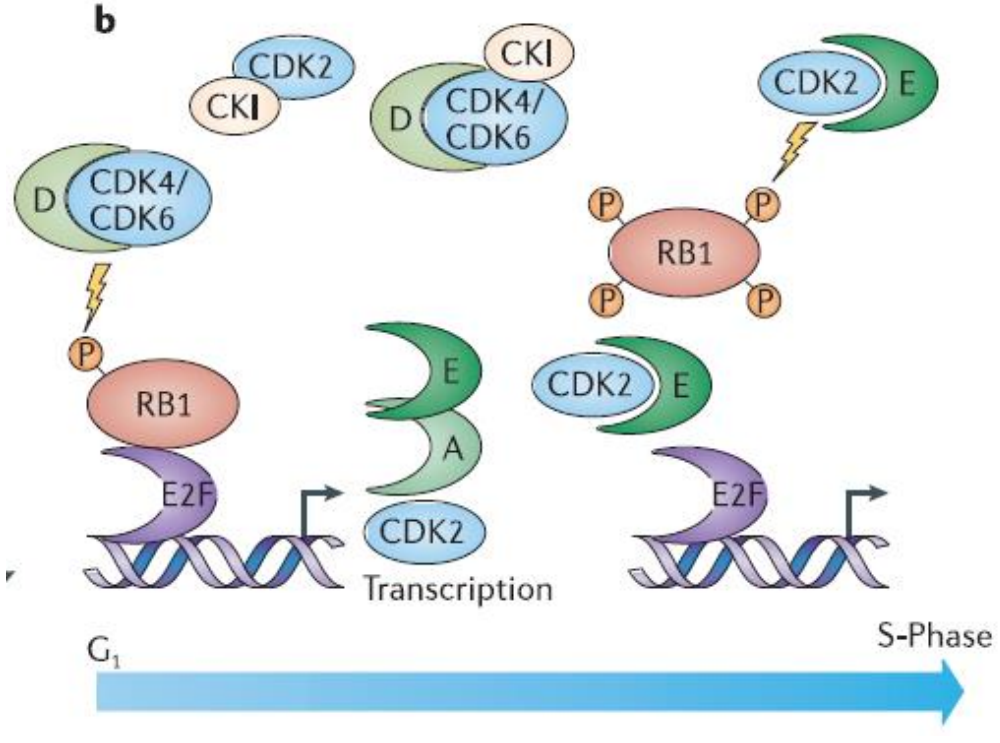
CDK4/6 biology: its role in cell cycle

- CDK4 and CDK6 belong to cyclin-dependent kinase family, which is critical for normal cell cycle progression from G1 to S phase. CDK4 and CDK6 share 71% amino acid identity and have largely overlapping functions.

- p16 (encoded by the CDKN2A gene) is an internal inhibitor of CDK4 and CDK6.



Cell Cycle

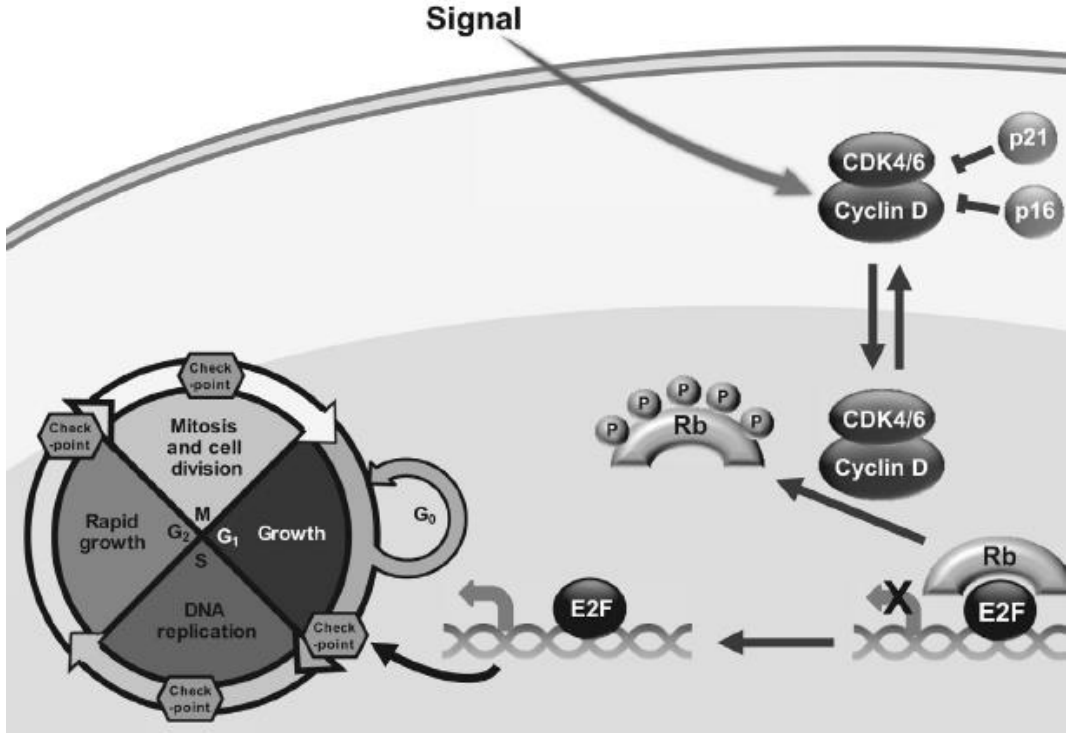


Classical model of G1-S phase transition

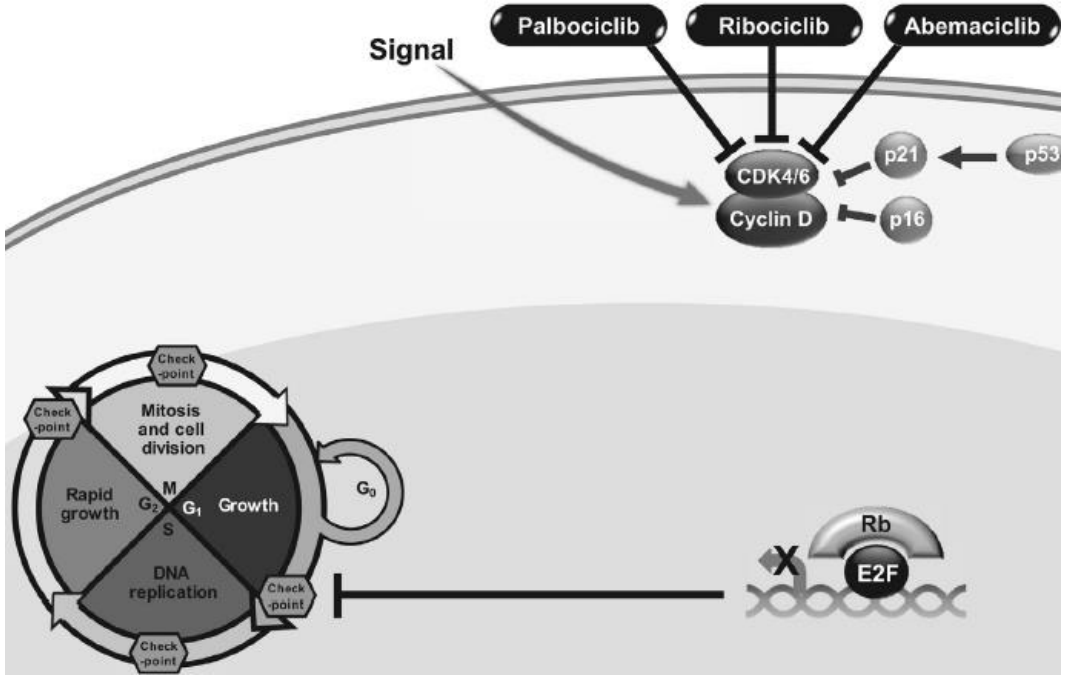
Nature Reviews Clinical Oncology (2016) doi:10.1038/nrclinonc.2016.26
Cancer Discov. 2016 Apr;6(4):353-67. doi: 10.1158/2159-8290.CD-15-0894

CDK4/6 biology: cyclin D-CDK4/6-INK4-Rb pathway

- Activated by proliferating signal, D-type cyclins associate with CDK4 or CDK6. These active cyclin D-CDK4/6 complexes phosphorylate retinoblastoma-associated protein Rb, releasing its inhibition on transcription factor E2F and promoting G1/S transition.
- CDK4/6 activity is regulated by INK4 family of proteins ($p16^{INK4A}$, $p15^{INK4B}$, $p18^{INK4C}$, and $p19^{INK4D}$). The INK4 proteins directly bind to CDK4/6 and inhibit their activity. Of the four INK4, $p16^{INK4A}$ is particularly important for tumor suppression.



(A) Overview of the cyclin D-CDK4/6-INK4-Rb pathway



(B) CDK4/6 inhibition results in decreased levels of phosphorylated Rb, promoting formation of Rb-E2F complexes and preventing E2F transcription factor activity

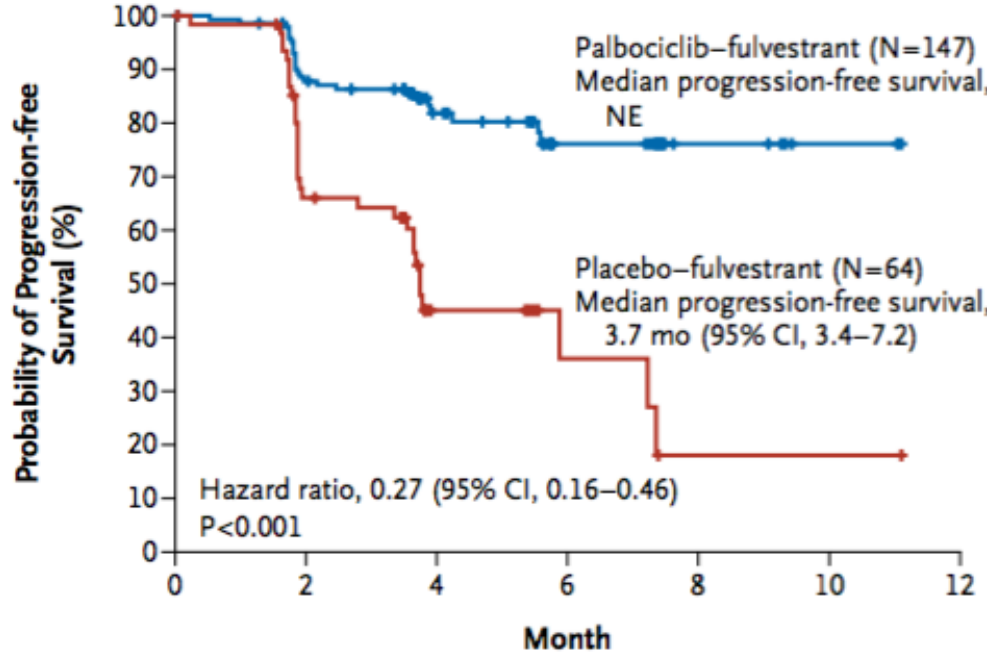
Cancer Treat Rev. 2016 Apr;45:129-38. doi: 10.1016/j.ctrv.2016.03.002.

The role of CDK4/6 signaling in cancer

- CDK4/6–cyclin D regulation is disrupted by several possible mechanisms:
  - i. Loss of CDK4 inhibitor p16 (CDKN2A) is a common event in many cancer types;
  - ii. Overexpression of cyclin D1: In mantle cell lymphoma, t(11;14)(q13;q32) translocation places cyclin D1 under the control of the immunoglobulin promoter;
  - iii. Amplification of CDK4: often seen in well-differentiated and dedifferentiated liposarcoma;
  - iv. Activating mutation of CDK4: Described in rare cases of familial melanoma.

- Selective CDK4/6 inhibitors are being evaluated in breast cancer, NSCLC, glioblastoma, liposarcoma, esophageal cancer, etc.

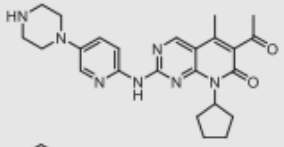
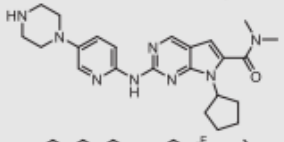
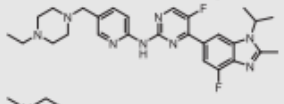
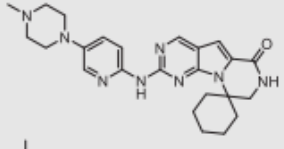
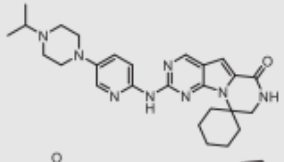
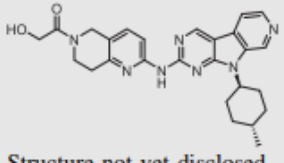
- Obvious efficacy was observed when ER+ breast cancer population was treated with CDK4/6 selective inhibitor + aromatase inhibitor, in contrast to placebo+ fulvestrant arm (right graph).



N Engl J Med 2015; 373:209-219
DOI: 10.1056/NEJMoa1505270

Clin Cancer Res. 2014 Jul 1;20(13):3379-83. doi: 10.1158/1078-0432.CCR-13-1551.

CDK4/6 inhibitors (approved or in clinical trials)

Name	Structure	Clinical status	Company
1 (Palbociclib)		Launched 2015	Pfizer
2 (Ribociclib)		Launched 2017	Novartis
3 (Abemaciclib)		Launched 2017	Lilly
4 (G1T28)		Phase II	G1 Therapeutics
5 (G1T38)		Phase I/II	G1 Therapeutics
6 (AMG 925)		Phase I	Amgen
SHR-6390	Structure not yet disclosed	Phase III	Hengrui
BPI-1178	Structure not yet disclosed	Phase I/II	Beta
BPI-16350	Structure not yet disclosed	Phase I/II	Betta
FCN 437	Structure not yet disclosed	Phase I	Fosun
Birociclib	Structure not yet disclosed	Phase I	Sihuan
BEBT-209	Structure not yet disclosed	Phase I	BeBetter
TY-302	Structure not yet disclosed	Phase I	TYK
TQB-3616	Structure not yet disclosed	Phase I	Chin Tai Tianqing
HS-10342	Structure not yet disclosed	Phase I	Hansoh
PF-06842874	Structure not yet disclosed	Phase I	Pfizer
CS-3002	Structure not yet disclosed	Phase I	Cstone
MM-D37K	Structure not yet disclosed	Phase I/II	MetaMax

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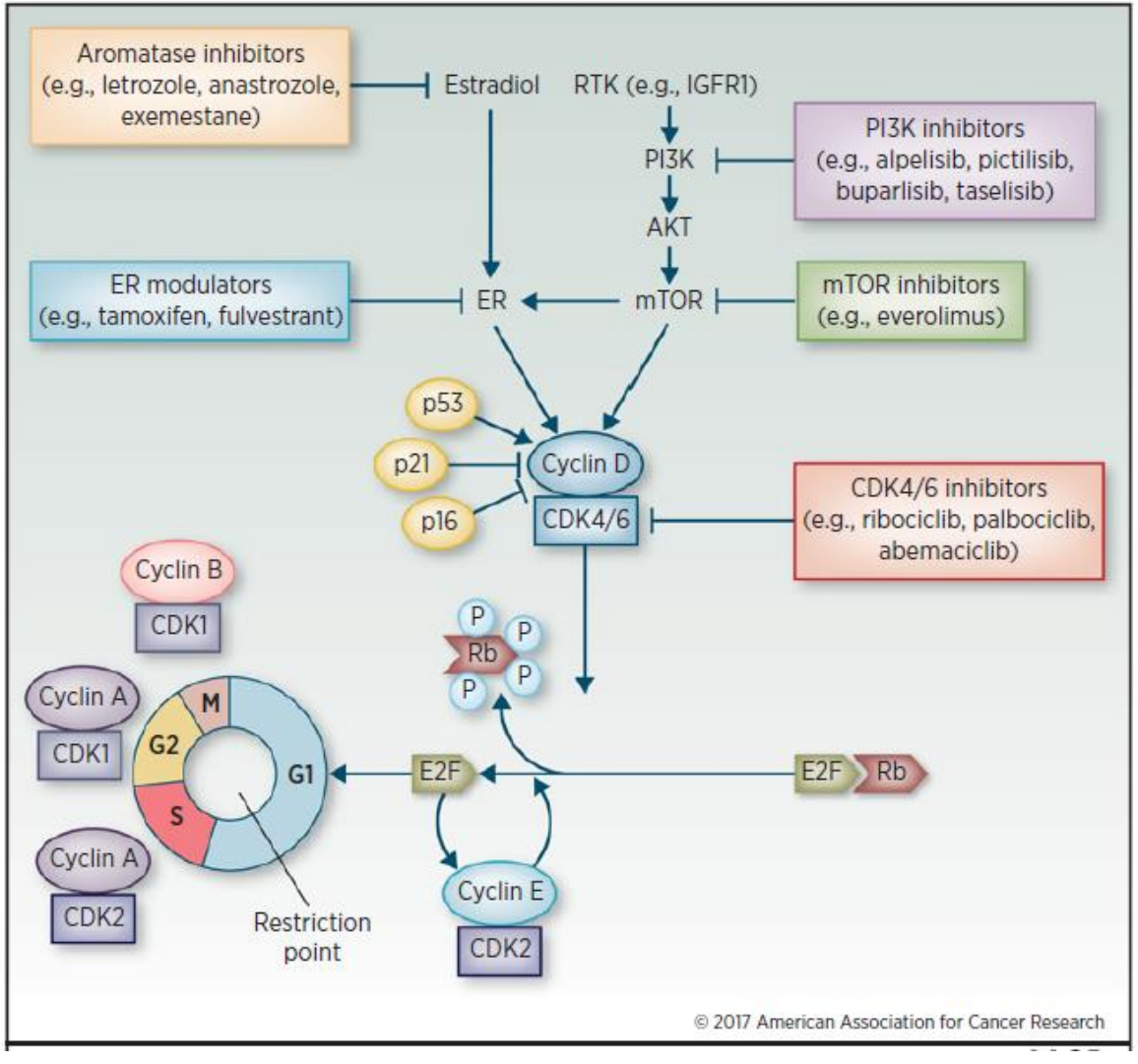
Cross-talk between ER, PI3K/mTOR and cyclin D–CDK4/6–Rb pathways



Clin Cancer Res; 23(13); 3251–62.

Currently registered clinical studies with CDK4/6 inhibitors

Compound	Study ID	Phase	Lines	Patients	Regimens	Efficacy
Palbociclib (PD-0332991)	PALOMA-1	II	First-line	HR+/HER2− ABC	Palbociclib + letrozole (n = 84)/letrozole (n = 81)	mPFS 20.2 m vs 10.2 m, HR 0.488, 95% CI 0.319–0.748, p = 0.0004
	PALOMA-2	III	First-line	HR+/HER2− ABC	Palbociclib + letrozole (n = 444)/letrozole (n = 222)	mPFS 24.8 m vs 14.5 m, HR 0.58, 95% CI 0.46–0.72, p < 0.001
	PALOMA-3	III	First/second-line	HR+/HER2− ABC with previous ET	Palbociclib + fluvastatin (n = 347)/fluvastatin (n = 174)	mOS 34.9 m vs 28.0 m, HR 0.81, 95% CI 0.64–1.03, p= 0.09
	NCT01684215	II	First-line	Postmenopausal Japanese patients with HR+/HER2− ABC	Palbociclib + letrozole (*n* = 42)	PFS at 1 year 75.0%, mPFS NR, ORR 40.5%, DCR 85.75%
	NCT02592746 (active, not recruiting)	II	First/second/third -line	Premenopausal Women With HR+ MBC	Palbociclib + exemestane + leuprolide acetate/capecitabine (*N* = 182)	mPFS 9.2 m vs 3.8 m, *p* < 0.001
	NCT01209598	II	Non-first line	Advanced WD/DDLS	Palbociclib (*n* = 60)	PFS at 12 weeks 57.2%; mPFS 17.9 weeks
	NCT02101034	II	Non-first line	HNSCCs	Palbociclib + cetuximab (*n* = 62)	ORR 39% (in platinum-resistant patients), ORR 19% (in cetuximab-resistant patients)
	NCT01037790 (recruiting)	II	UK	RB/germ cell tumors	Palbociclib (*n* = 205)	PFS at 6 months 28%; mPFS 11 weeks
	NCT01536743 (active, not recruiting)	II	Non-first line	Ovarian epithelial carcinoma	Palbociclib (*n* = 26)	PFS at 6 months 15%
	NCT00420056	Ib	UK	MCL	Palbociclib (*n* = 17)	6% CR, 12% PR, 41% SD, mPFS 4.0 m

J Hematol Oncol **13,** 41 (2020). https://doi.org/10.1186/s13045-020-00880-8

Currently registered clinical studies with CDK4/6 inhibitors

Compound	Study ID	Phase	Lines	Patients	Regimens	Efficacy
Ribociclib (LEE011)	MONALEESA-2	III	First-line	Postmenopausal women with HR+/HER2− ABC	Ribociclib + letrozole (*n* = 334)/letrozole (*n* = 334)	mPFS NR vs 14.7 m, HR 0.56, 95% CI 0.43–0.72, $p < 0.001$
	MONALEESA-3	III	First/second-line	HR+/HER2− ABC	Ribociclib + fulvestrant (*n* = 484)/fulvestrant (*n* = 242)	mPFS 20.5 m vs 12.8 m, HR 0.59, 95% CI 0.48–0.73, $p < 0.001$
	MONALEESA-7	III	First/second-line	Premenopausal women with HR+/HER2− ABC	Ribociclib + ET (*n* = 335)/ET (*n* = 337)	mPFS 23.8 m vs 13.0 m, HR 0.55, 95% CI 0.44–0.69, $p < 0.001$
	TRINITI-1 NCT02732119 (active, not recruiting)	I/II	Non-first line	Patients with HR+/HER2− ABC	Ribociclib + everolimus + exemestane (*n*= 107)	mPFS 5.7 m, ORR 8.4%
	CLEE011X2105	Ib/II	Non-first line	BRAF V600-mutant melanoma	Ribociclib (*n*= 18)	2 PR, 6 SD
	CMEK162X2114	Ib/II	UK	NRAS-mutant melanoma	Ribociclib + binimetinib (*n* = 22)	7 PR, 11 SD, 33% had 20–30% tumor shrinkage
Abemaciclib (LY2835219)	MONARCH-1	II	Non-first line	Refractory HR+/HER2− ABC	Abemaciclib (*n* = 132)	ORR 19.7%, clinical benefit rate (CR + PR + SD ≥ 6.0 m) 42.4%, mPFS 6.0 m, mOS 17.7 m
	MONARCH-2	III	Non-first line	HR+/HER2− ABC	Abemaciclib + fulvestrant (*n* = 446)/fulvestrant (*n* = 223)	mPFS 16.4 m vs 9.3 m, HR 0.55, 95% CI 0.45–0.68, $p< 0.001$
	MONARCH 3	III	First-line	Postmenopausal women with HR+/HER2− ABC	Abemaciclib + nonsteroidal AI (*n* = 223)/nonsteroidal AI (*n* = 223)	mPFS NR vs 14.7 m, HR 0.54, 95% CI 0.41–0.72, $p < 0.001$, ORR 59% vs 44%, $p = 0.004$
	NCT01394016	I	UK	Breast cancer; NSCLC; Melanoma; Glioblastoma; CRC	Abemaciclib (*n* = 225)	Breast cancer (*n* = 47) 23% PR, 47% SD, 23% ORR, 49% CBR, 70%DCR, mPFS 5.8 m; NSCLC (*n* = 68), 3% PR, 46% SD, 3% ORR, 49% DCR, mPFS 2.0 m; melanoma (*n* = 26) 4% PR, 23% SD, 4% ORR, 27% DCR; glioblastoma (*n* = 17) 18% SD, 18% DCR; CRC (*n* = 15) 13% SD, 13% DCR
	NCT02014129	I	Non-first line	Various advanced cancer	Abemaciclib (*n* = 12)	tumor size changed from 35% decrease to 25% increase, > 30% tumor shrinkage in 2 patients

J Hematol Oncol **13,** 41 (2020). https://doi.org/10.1186/s13045-020-00880-8

Investigational clinical trials with Abemaciclib (excluding MONARCH 1, 2 and 3)

Trial ID	Phase	Tumor type	Population	Therapies	Primary outcome
NCT03155997/MONARCH E	III	HR+/HER2− BC	High risk, node positive, early stage	Abemaciclib ± standard endocrine therapy	IDFS
NCT02779751	I	HR+/HER2− BC	mBC	Abemaciclib ± pembrolizumab	SAEs
NCT02747004	II	HR+/HER2− BC	Previously treated mBC	Abemaciclib ± tamoxifen	PFS
NCT02831530/ABC-POP	II	HR+/HER2− BC	Neoadjuvant early BC	Abemaciclib	Antiproliferative response
NCT02763566/MONARCH Plus	III	HR+/HER2− BC	Postmenopausal women with locoregional recurrence or mBC	Abemaciclib ± NSAIs Abemaciclib ± fulvestrant	PFS
NCT02308020	II	Brain metastases secondary to HR+/HER2± BC	mBC	Abemaciclib	CR or PR: OIRR
NCT02675231/monarcHER	II	HR+/HER2+ BC	Locally advanced BC or mBC. Two previous lines of anti-HER2 therapy	Abemaciclib + trastuzumab ± fulvestrant	PFS
NCT02057133	I	HR+/HER2− BC	mBC	Abemaciclib + letrozole or anastrozole or tamoxifen or exemestane and/or everolimus or trastuzumab or LY3023414 or fulvestrant	SAEs
NCT03099174	I	HR+/HER2− BC	Advanced BC or mBC	Abemaciclib + xentuzumab ± endocrine therapy	MTD, DLT, CR and PR as per RECIST version 1.1 (MONALEESA-3)
NCT02791334/PACT	I	HR+/HER2− BC	Advanced refractory BC	Abemaciclib + LY3300054	DLT
NCT02784795	I	HR+/HER2− BC and TNBC	Notch pathway-related alterations	Abemaciclib + LY3039478	MTD
NCT01655225	I	HR+/HER2− BC	Locally advanced BC or mBC	Abemaciclib + LY3023414 + letrozole	Recommended dose
NCT03130439	II	TNBC	Rb-positive, triple negative metastatic BC	Abemaciclib	ORR

Adapted from Drug Des Devel Ther. 2018 Feb 16;12:321-330.

CDK4/6-related CDX models

Cancer type	Model ID	Model at WuXi (Y/N)	Study Reported in Literatures	Dosing Regimen Reported	TGI (Efficacy) Reported	WuXi Efficacy Studies	Model Genetics
Liposarcoma	LP6	N	Ribociclib[1]	250 mg/kg, QD	70%	NA	CDK4 overexpression
Glioblastoma	U87MG (subQ)	Y	Abemaciclib[5]	100 mg/kg, QD	~100%	NA	CDKN2A/B, CDKN2C: homozygous deletion[4]
	U87MG-Luc (Orthotopic)	Y	Abemaciclib[4]	150 mg/kg, QD	Normalized luminescence: > 90% inhibition	Yes	CDKN2A/B, CDKN2C: homozygous deletion
Breast cancer	MCF-7	Y	-	-	-	Yes	ER positive p16 deletion
Colorectal cancer	Colo 205	Y	Palbociclib[2]	150 mg/kg, QD	> 100%	Yes	Rb positive
Melanoma	A375	Y	Abemaciclib[3]	100 mg/kg, QD	> 70%	NA	NA
Leukemia	MV-4-11	Y	Abemaciclib[5]	100 mg/kg, QD	> 90%	Yes	Rb positive

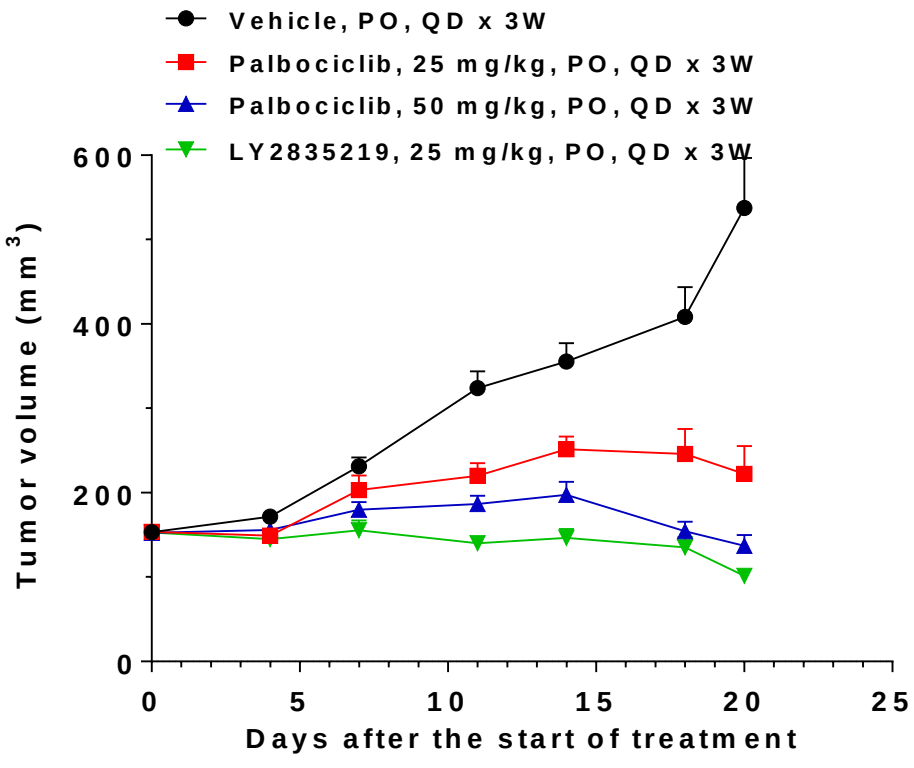
Mol Cancer Ther. 2014 Sep;13(9):2184-93.
Mol Cancer Ther. 2004 Nov;3(11):1427-38.
Clin Cancer Res. 2014 Jul 15;20(14):3763-74.
Cancer Res. 2010 Apr 15;70(8):3228-38.
Invest New Drugs. 2014 Oct;32(5):825-37.

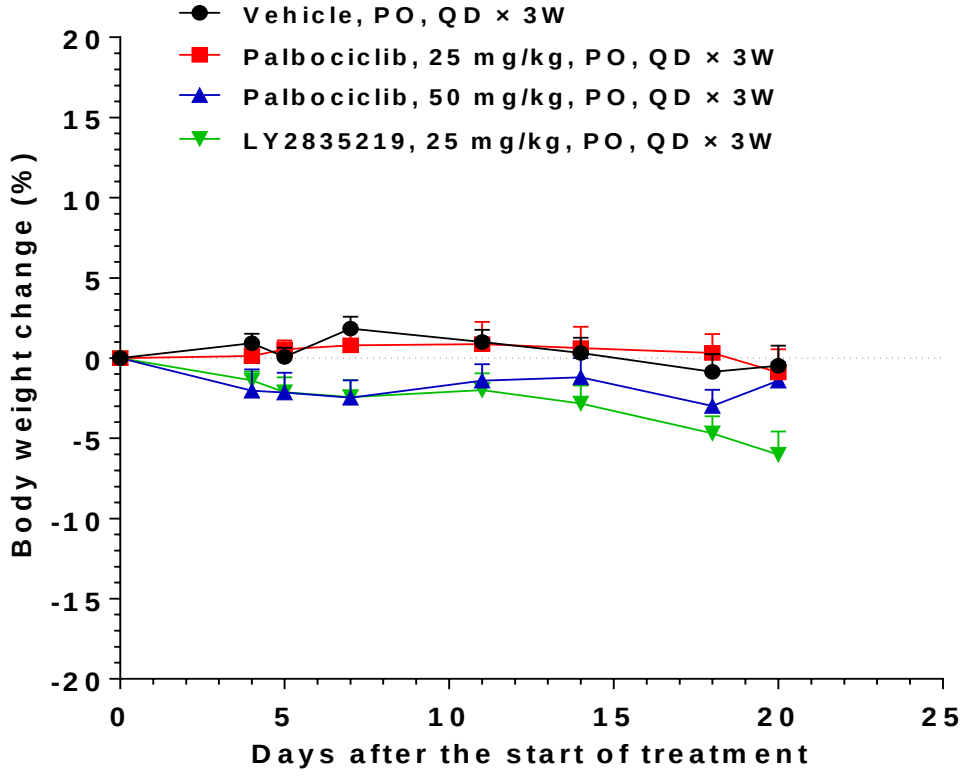
CDK4/6-related CDX models

Cancer type	Model ID	Model at WuXi (Y/N)	Study Reported in Literatures	Dosing Regimen Reported	TGI (Efficacy) Reported	WuXi Efficacy Studies	Model Genetics
Lung	NCI-H2122	Y	Palbociclib	NA	NA	Yes	
Breast	xZR-75-1	Y	Palbociclib[1]	150 mg/kg, QD	~100%	Yes	Rb positive
Breast	xxT47D	Y	Palbociclib	NA	NA	Yes	Rb positive
Liver	Huh-7	Y	Palbociclib	NA	NA	Yes	
NSCLC	NCI-H358	Y	Palbociclib	NA	NA	Yes	Rb positive;
			LY2835219	NA	NA	Yes	

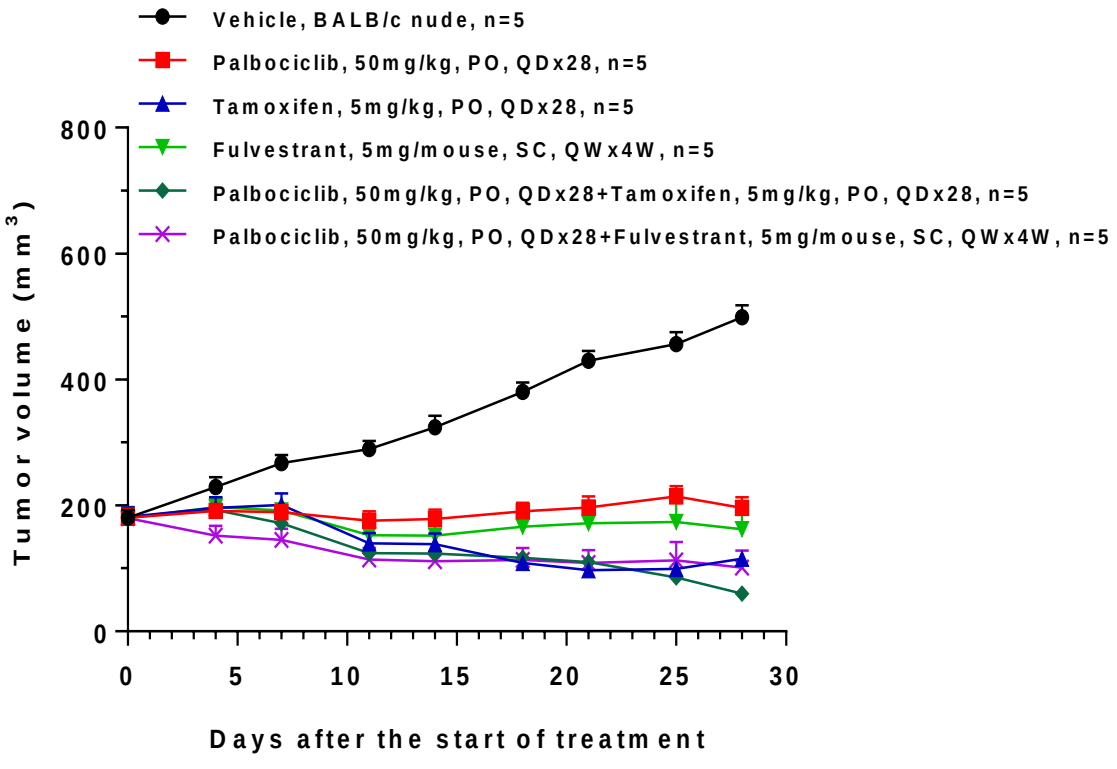
Mol Cancer Ther. 2004 Nov;3(11):1427-38.

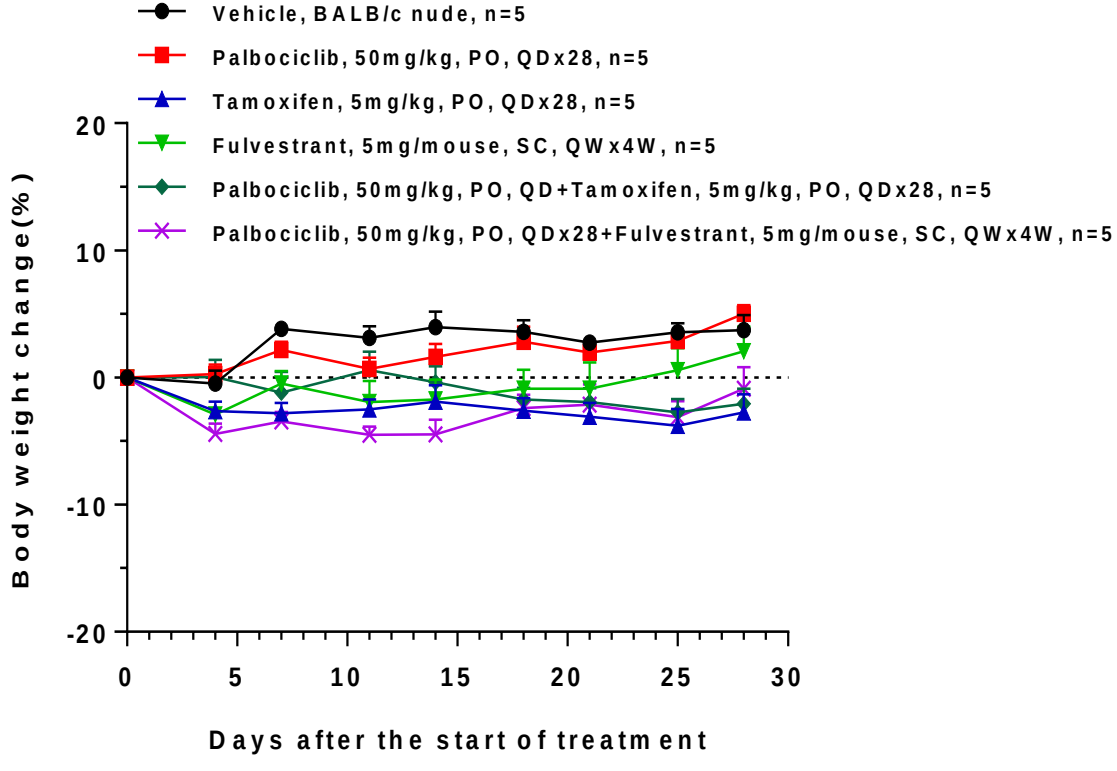
CDK4/6 inhibitors in MCF-7 CDX model



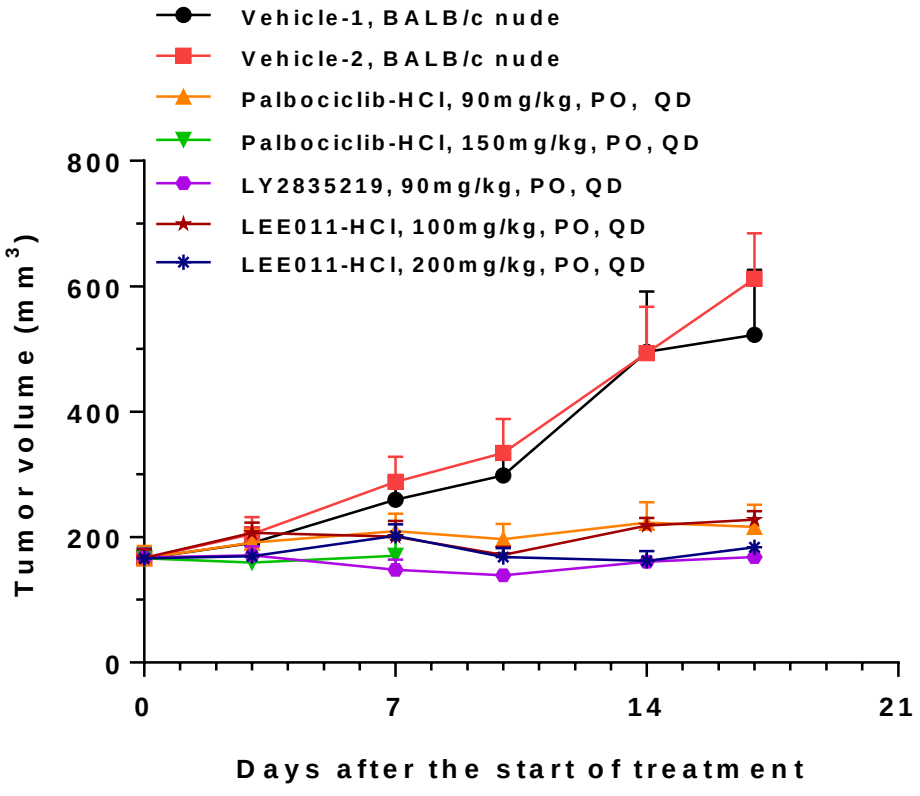


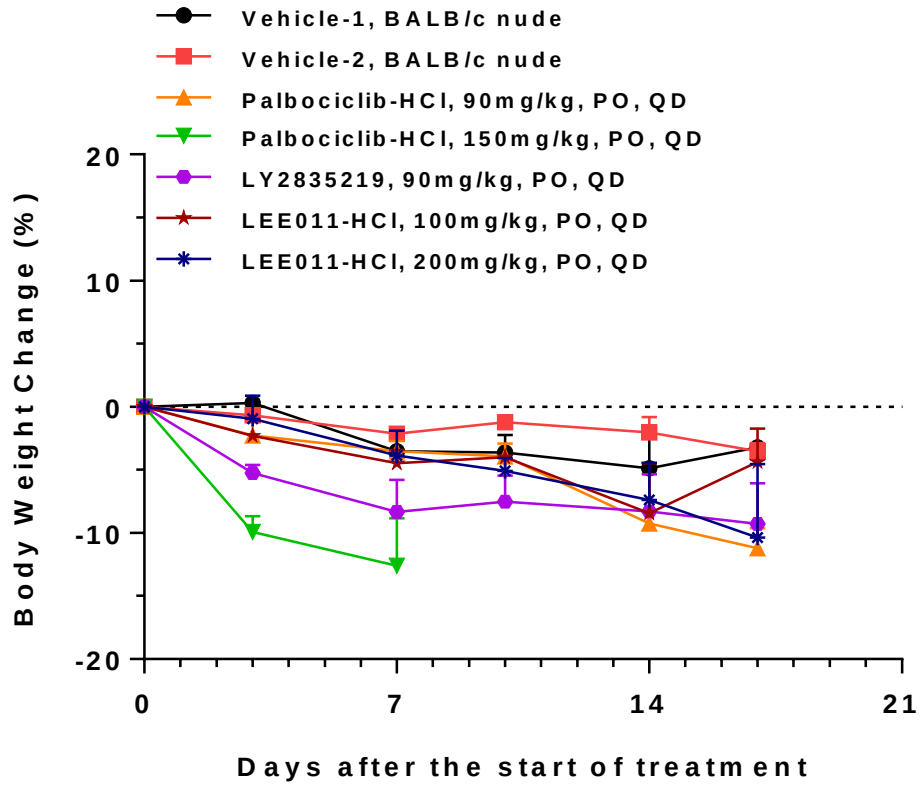
CDK4/6 inhibitors in MCF-7 CDX model



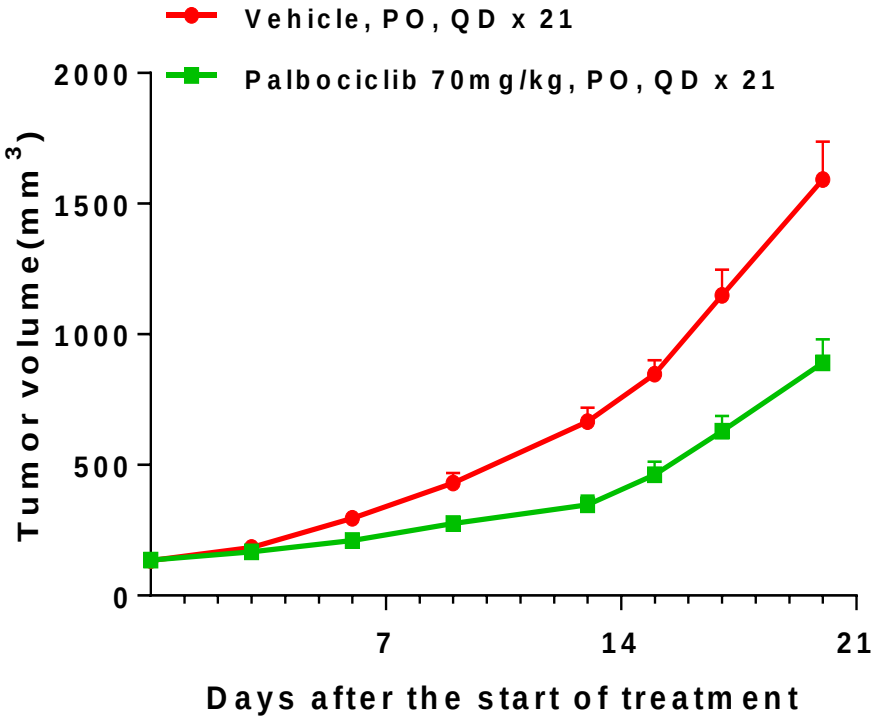


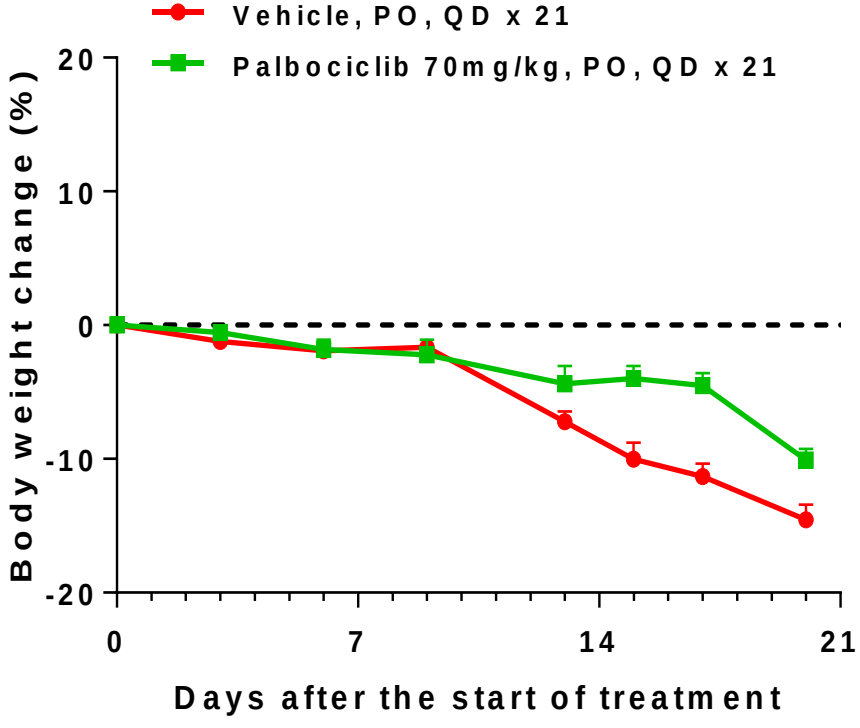
CDK4/6 inhibitors in MCF-7 CDX model



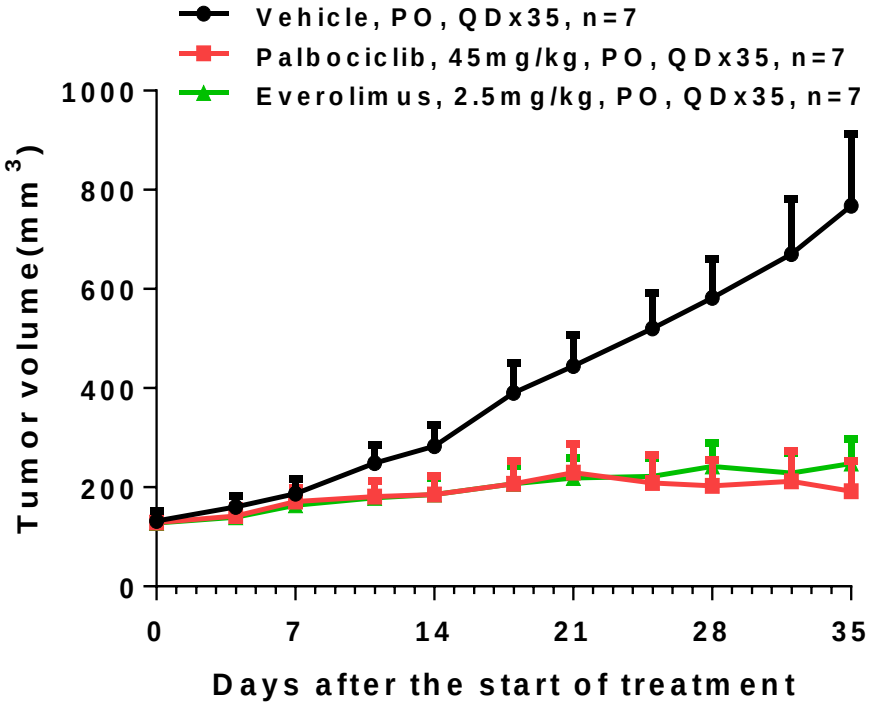


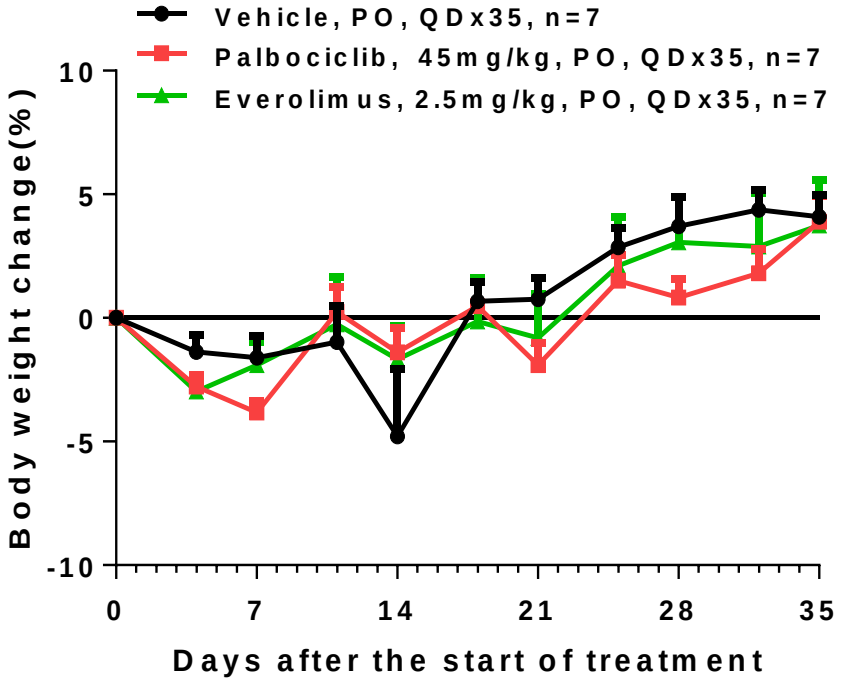
CDK4/6 inhibitors in NCI-H2122 CDX model



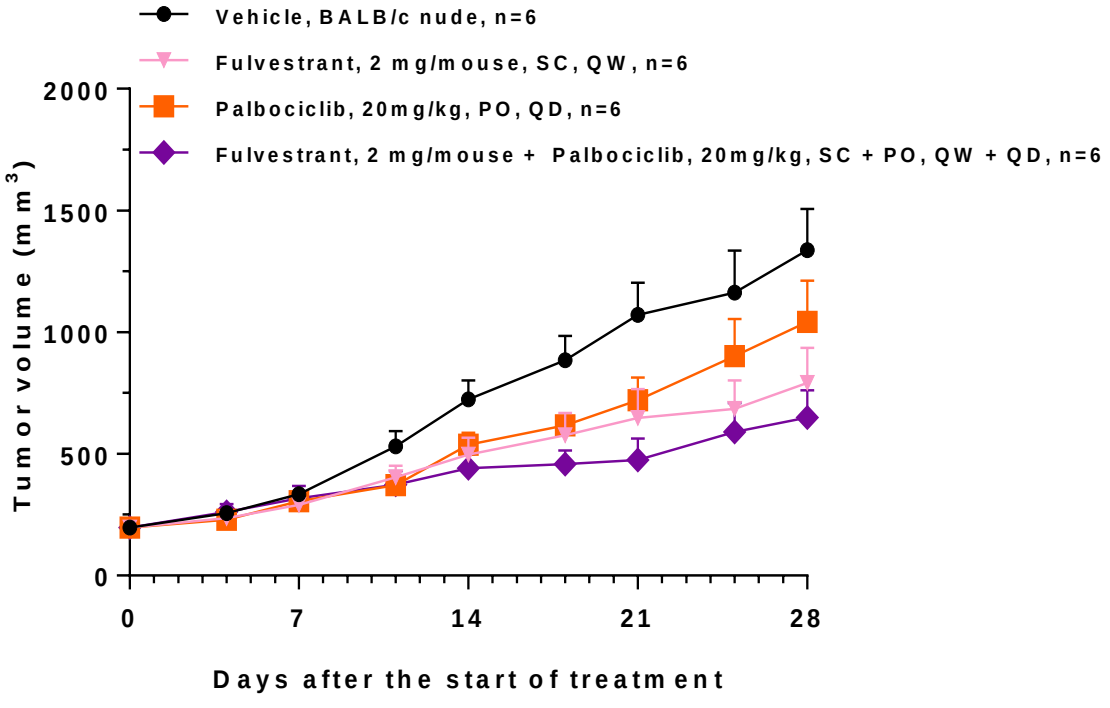


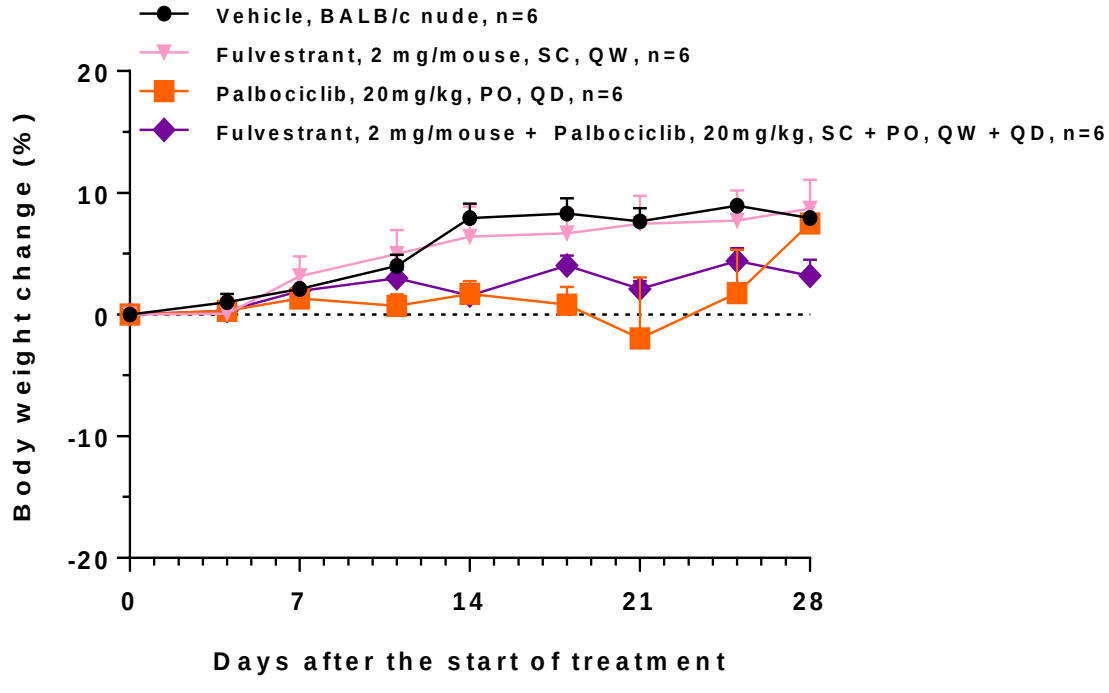
CDK4/6 inhibitors in xZR-75-1 CDX model



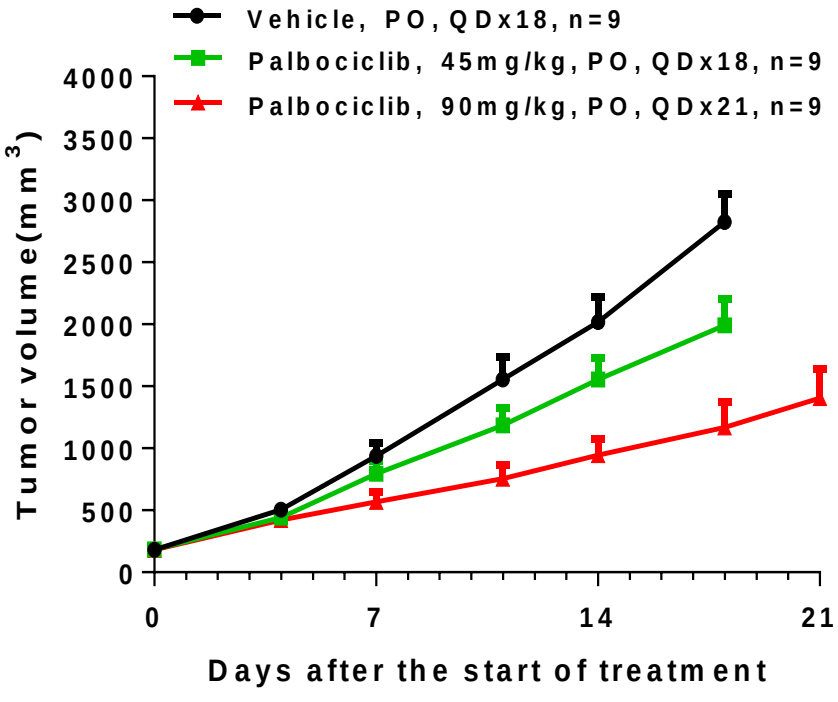


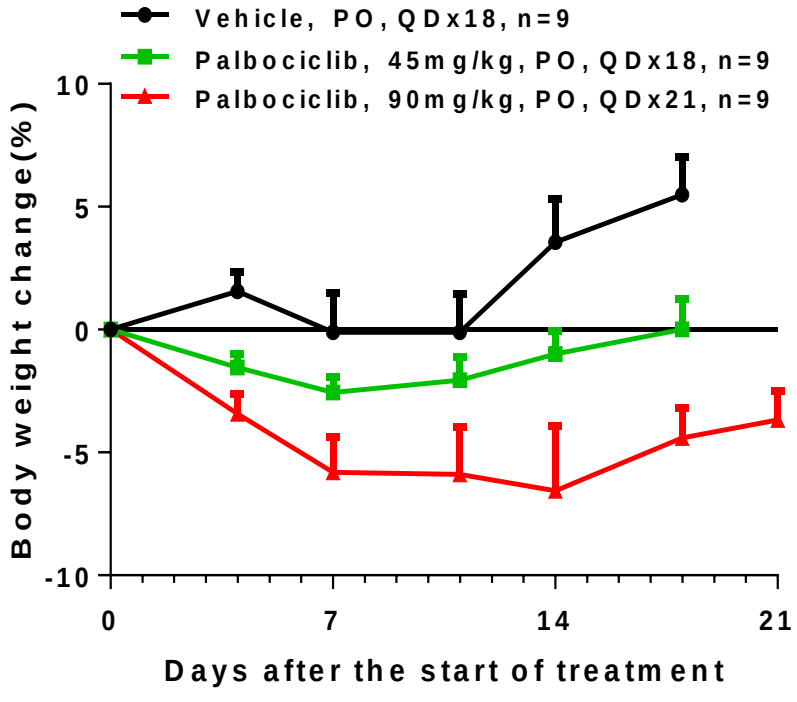
CDK4/6 inhibitors in xxT47D CDX model



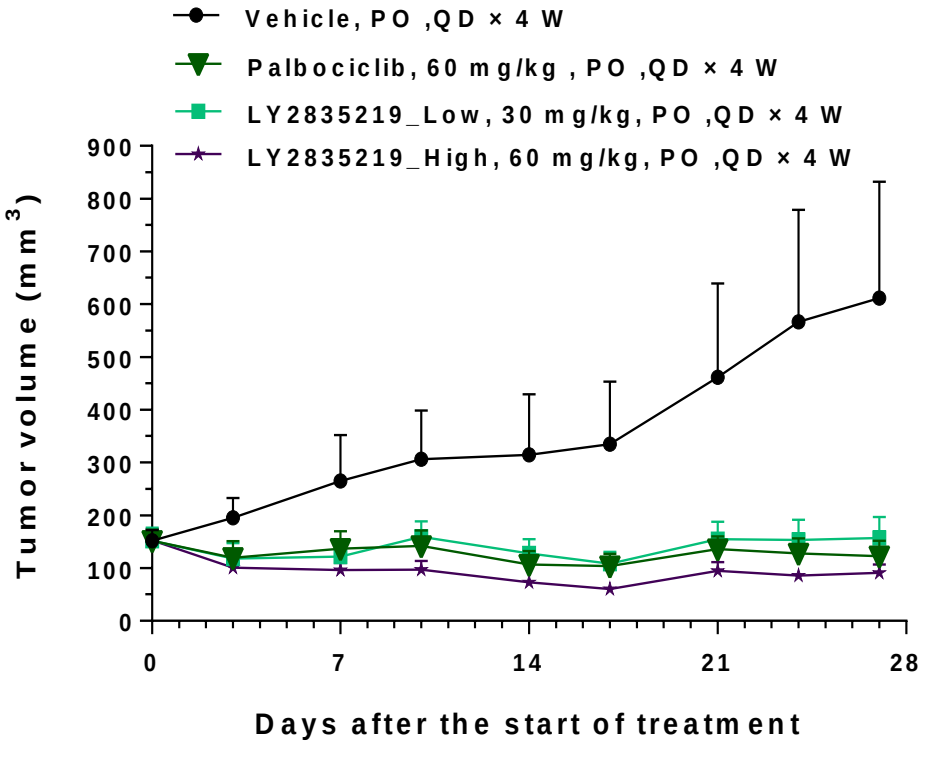


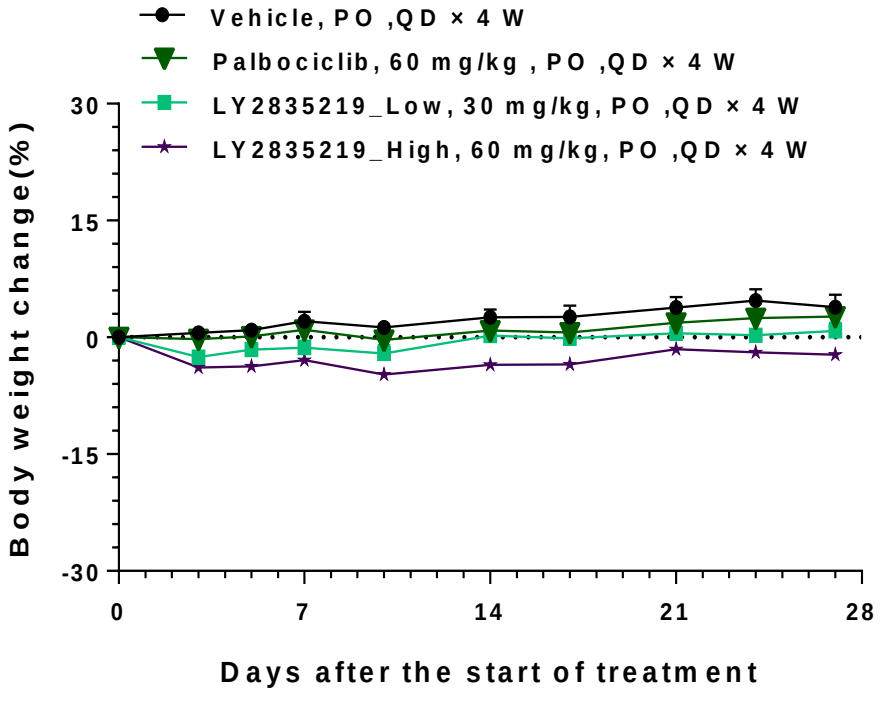
CDK4/6 inhibitors in Huh-7 CDX model



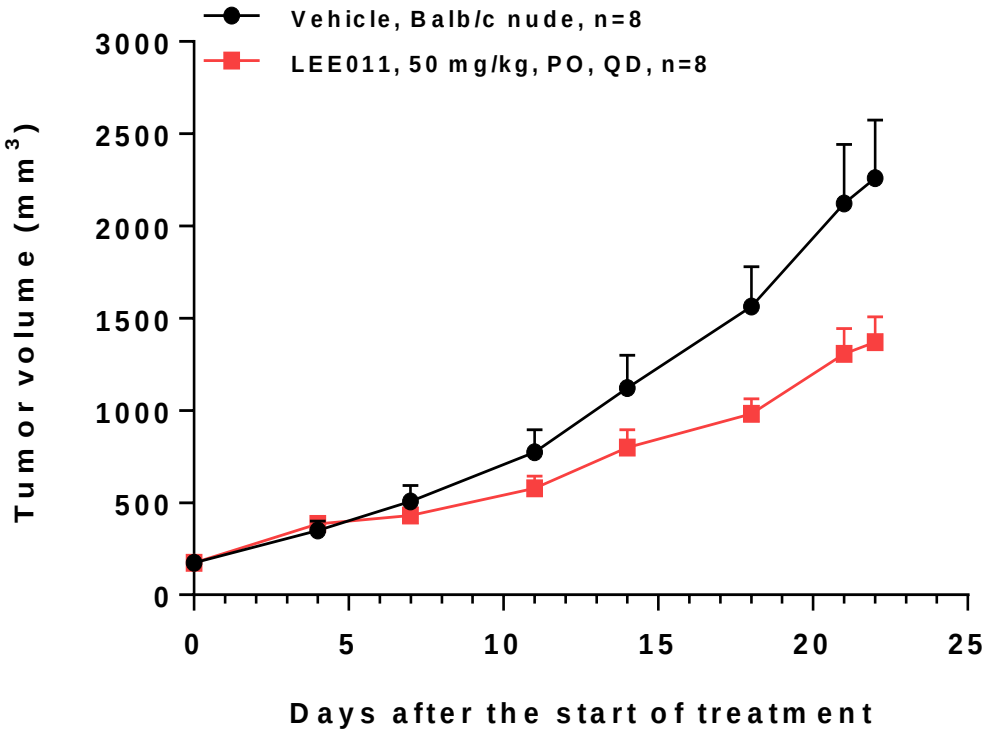


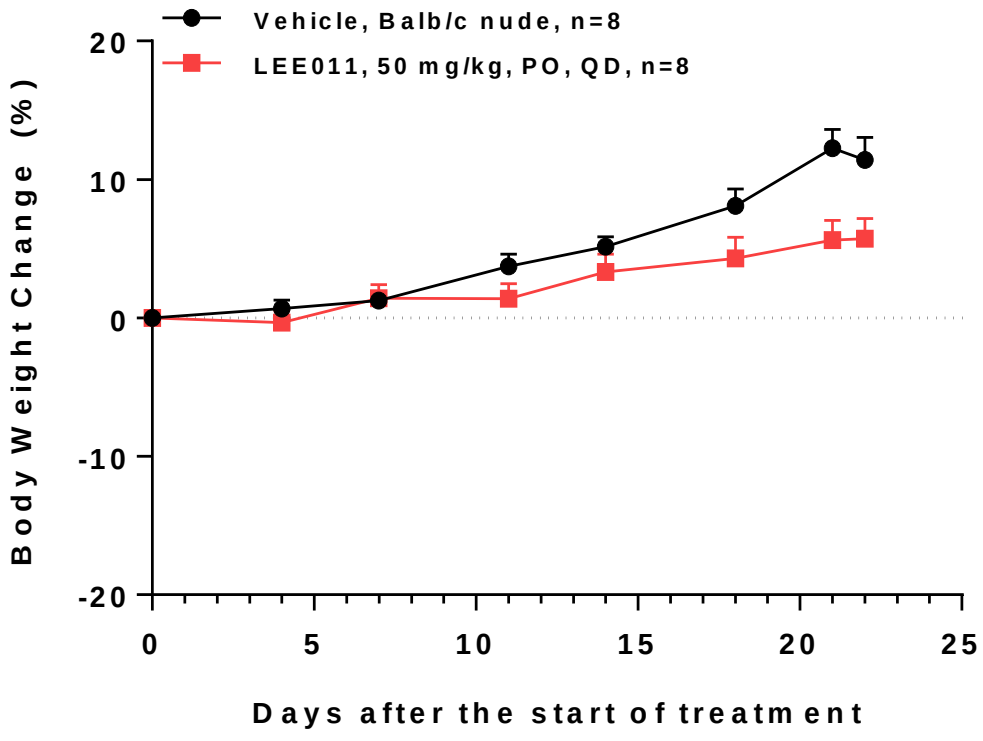
CDK4/6 inhibitors in NCI-H358 CDX model



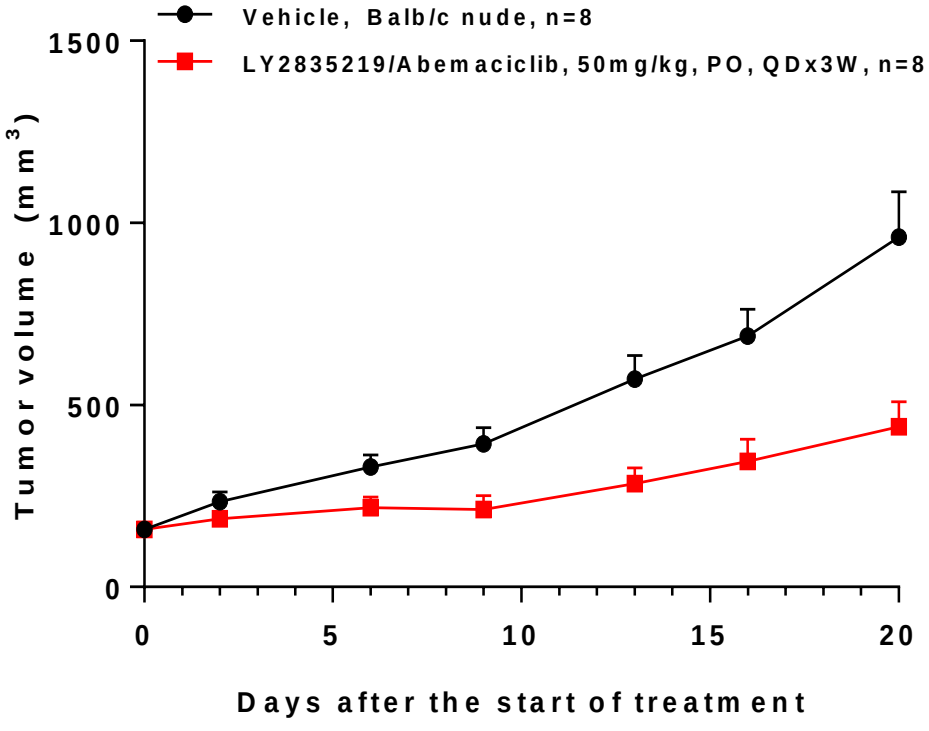


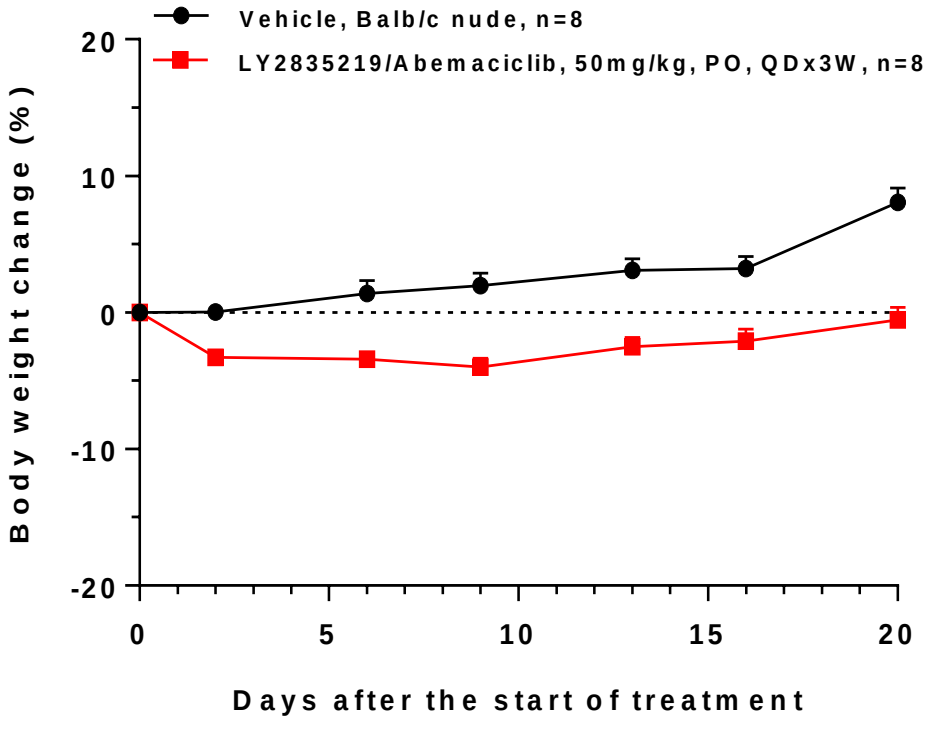
CDK4/6 inhibitors in MV-4-11 CDX model



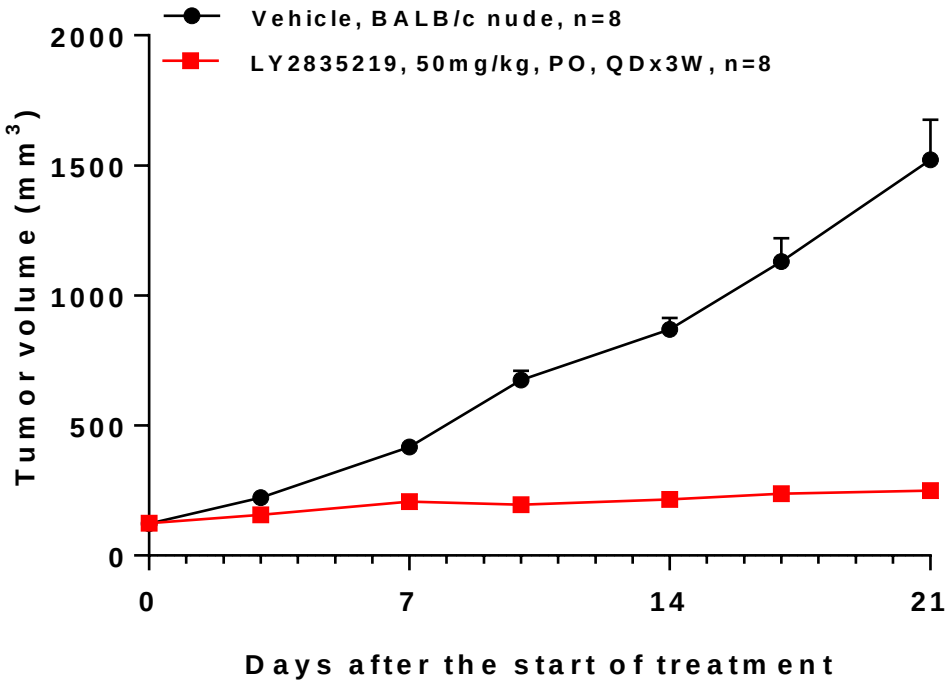


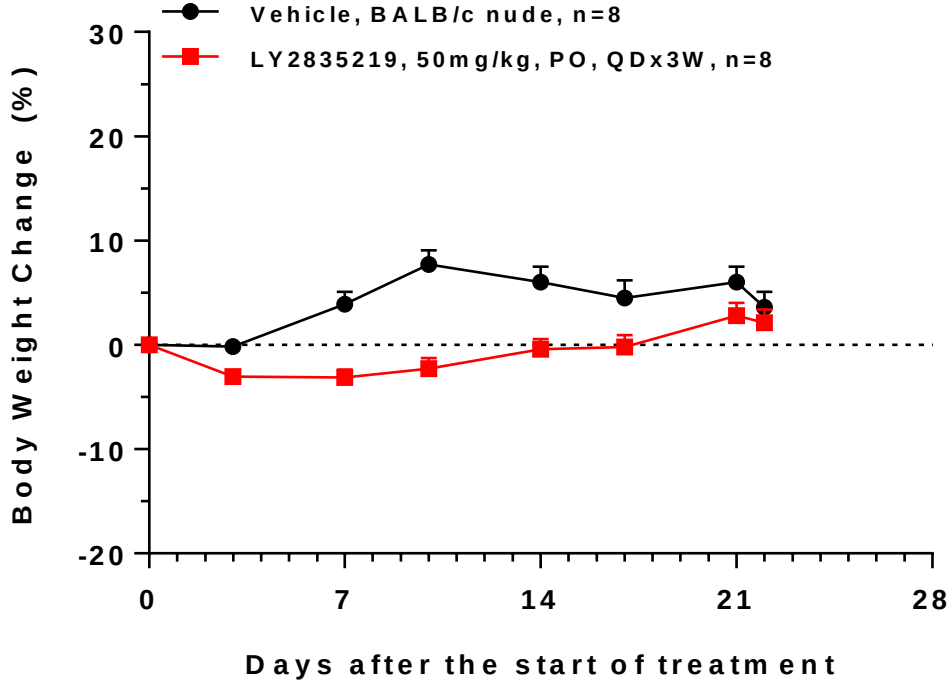
CDK4/6 inhibitors in MV-4-11 CDX model



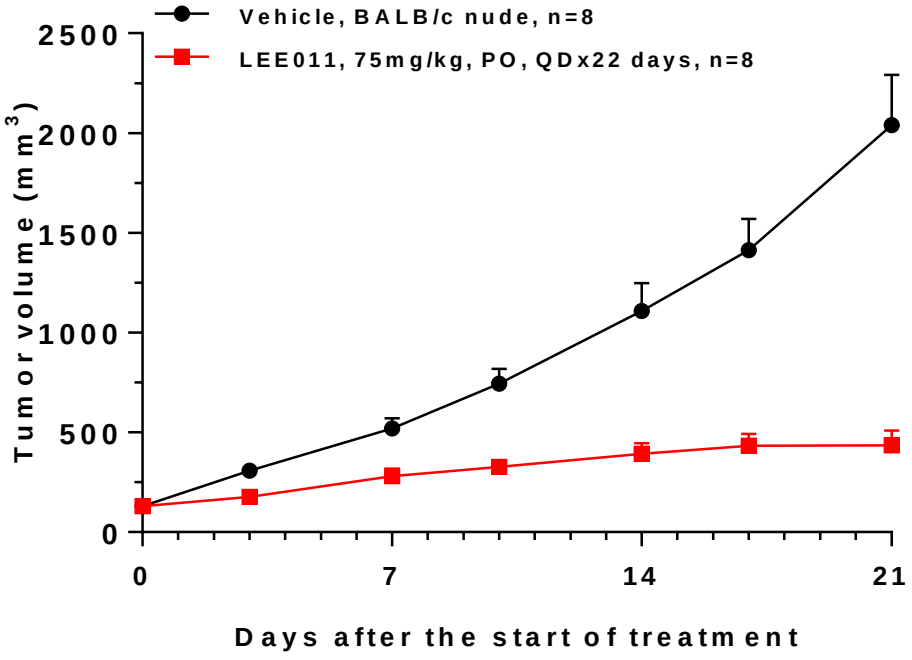


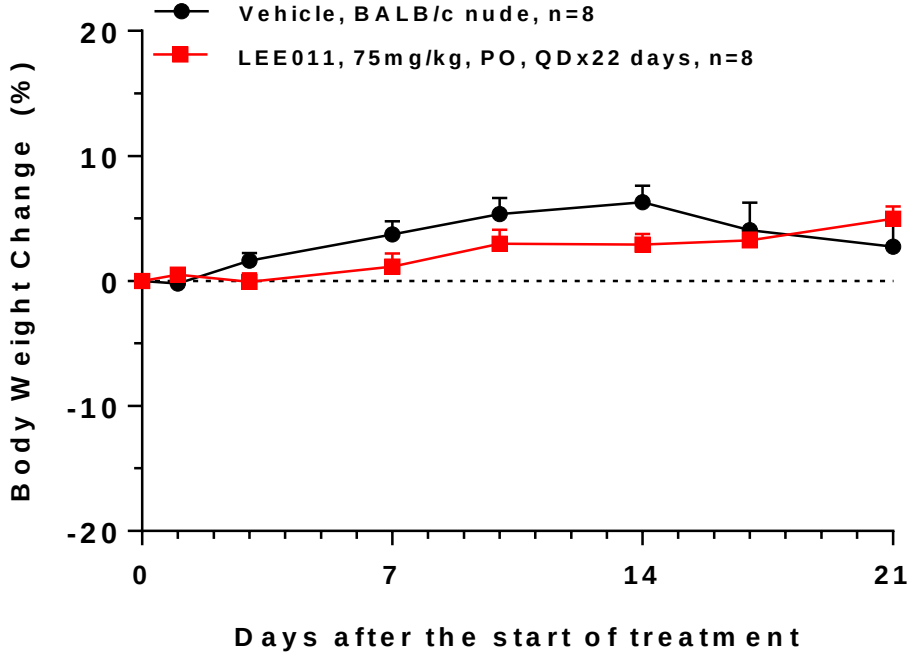
CDK4/6 inhibitors in Colo 205 CDX model



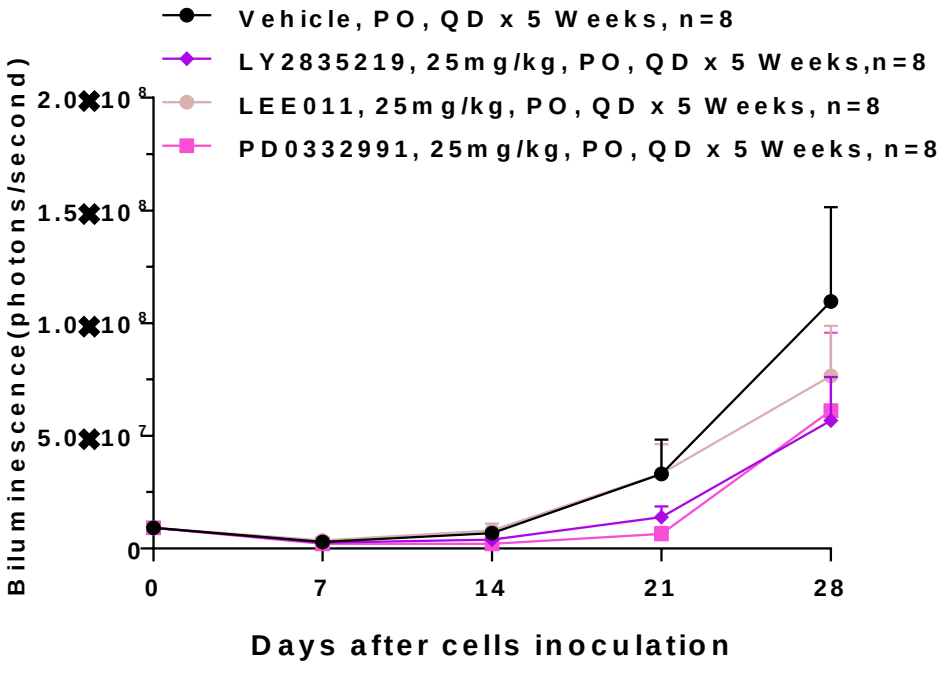


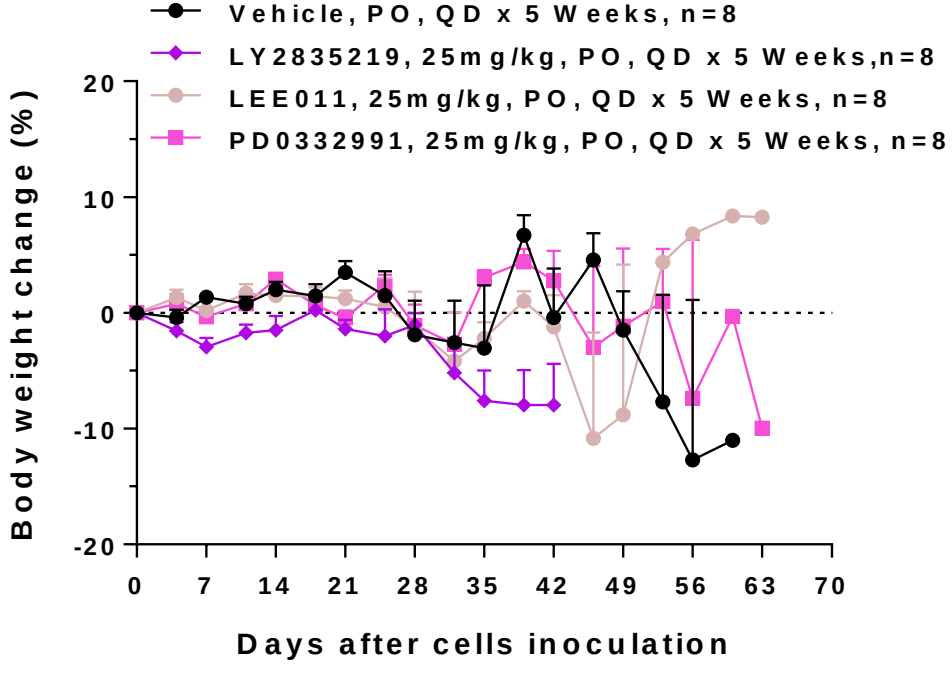
CDK4/6 inhibitors in Colo 205 CDX model





CDK4/6 inhibitors in U87-Luc orthotopic CDX model





CDK4/6 inhibitors in U87-Luc orthotopic CDX model

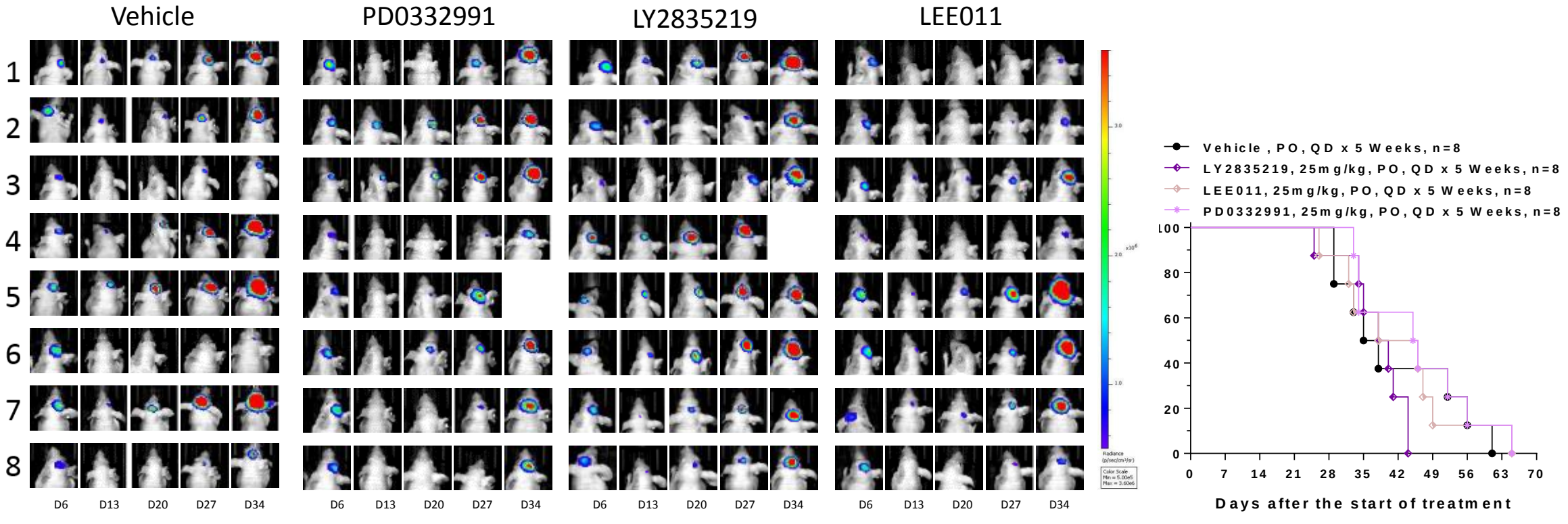
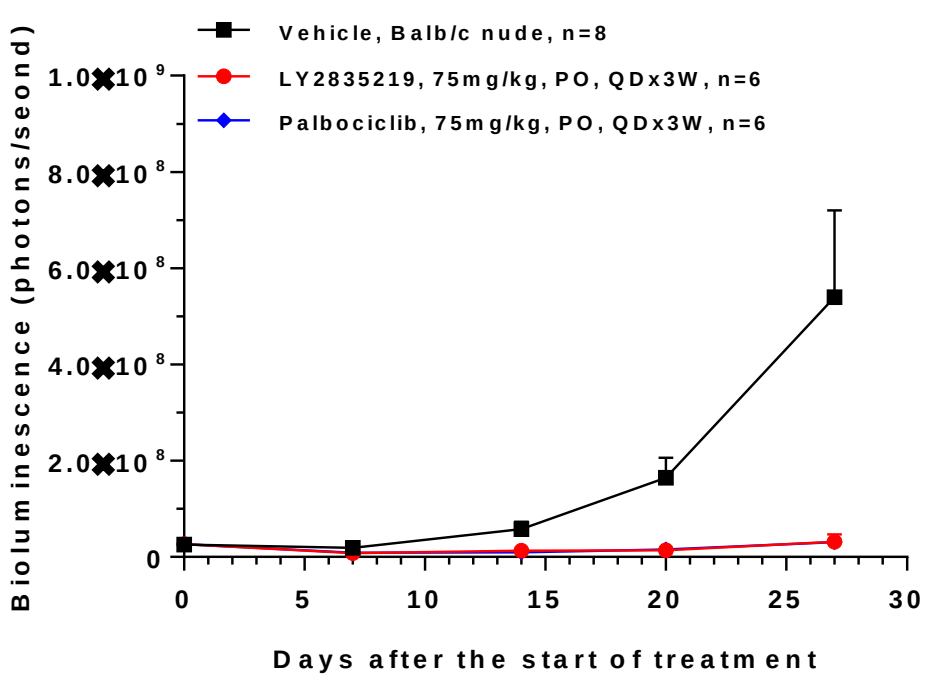
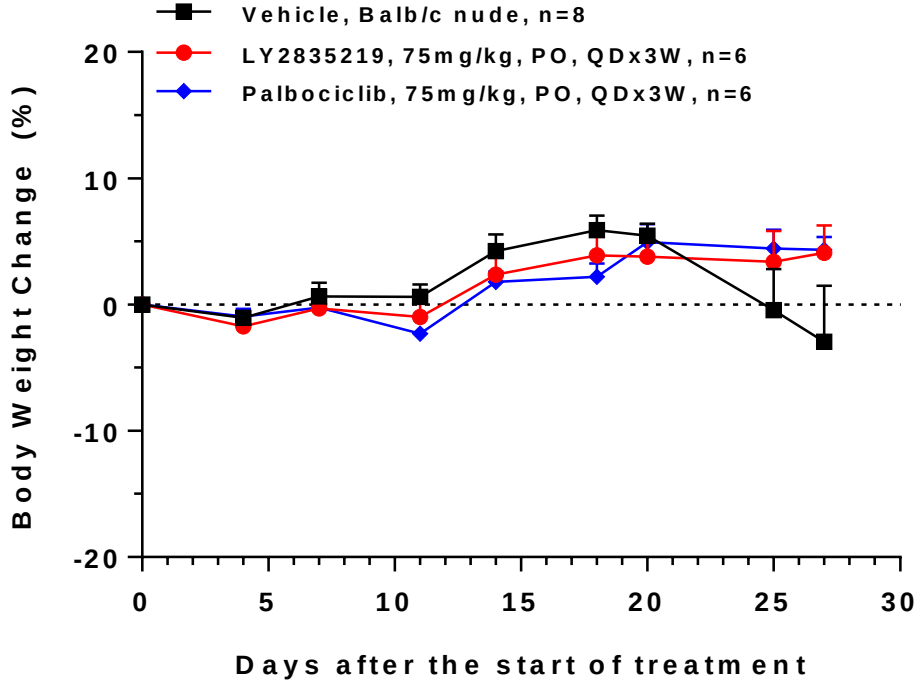


Figure: Validation of U87-luc-based orthotopic models with PD0332991, LY2835219 and LEE011. Bioluminescent imaging of nude mice injected with U87-luc orthotopically on day 0 and treated with either vehicle, PD0332991, LY2835219 or LEE011 from day 6. n=8 for each group.

CDK4/6 inhibitors in the U87-luc orthotopic model

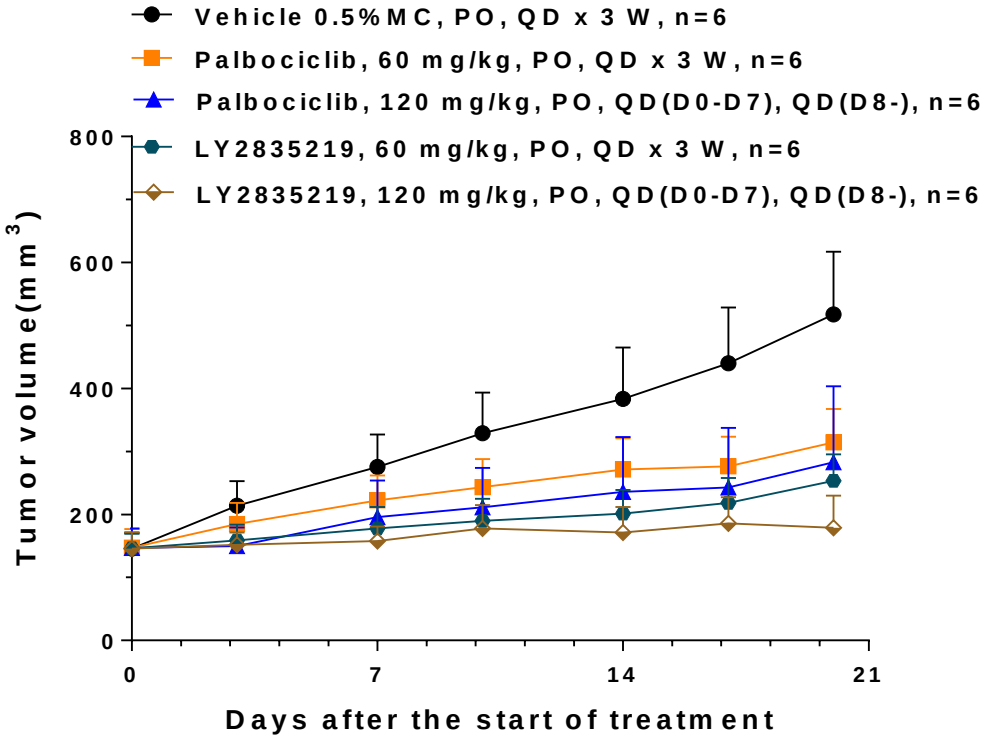


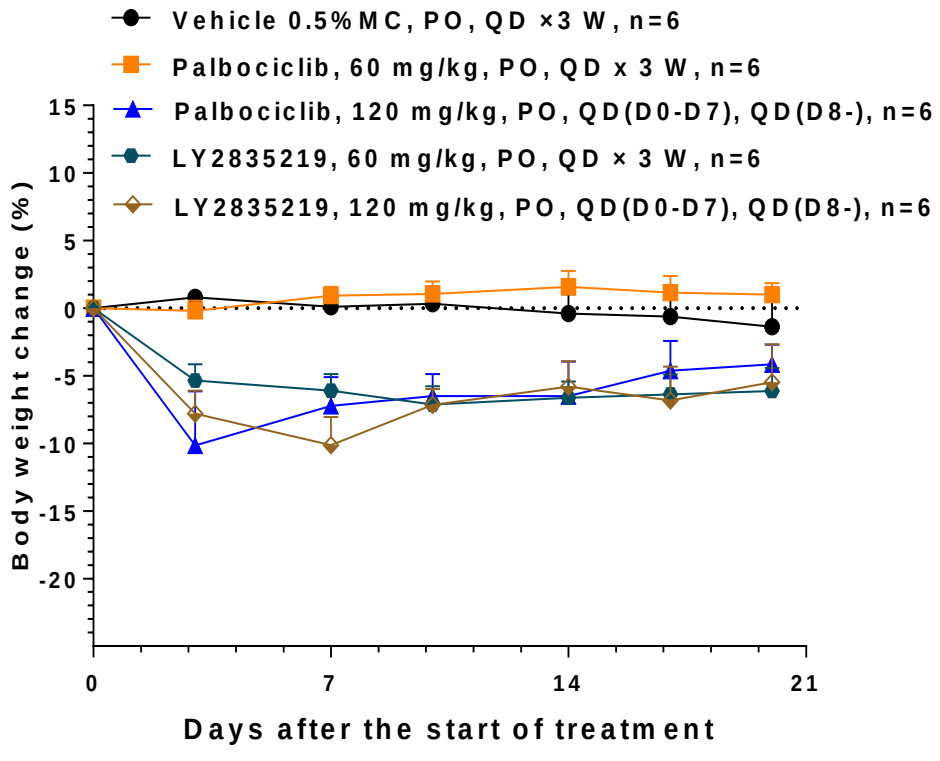


CDK4/6-related PDX models

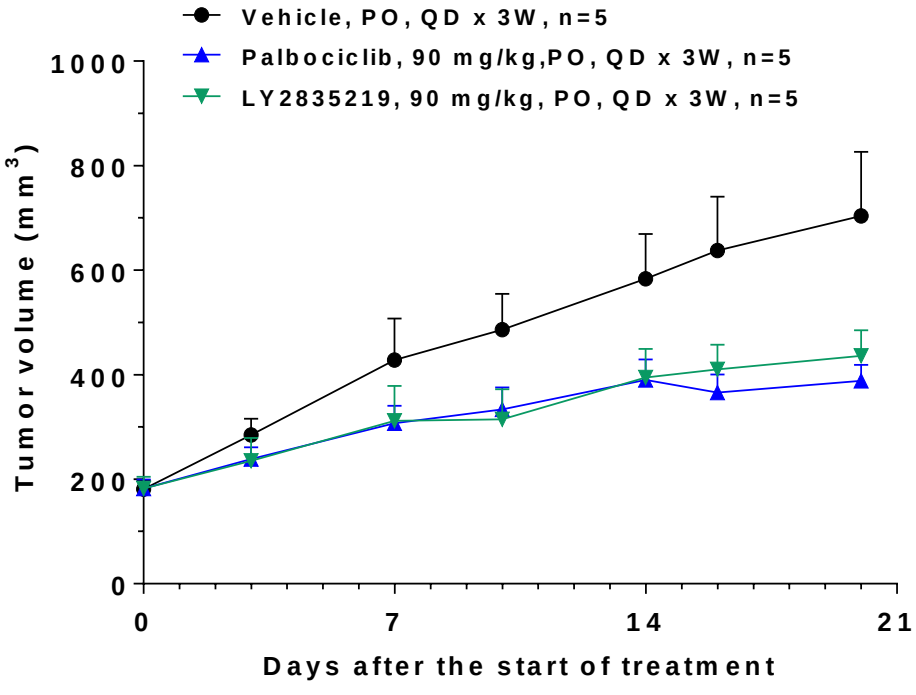
Model ID	Cancer type	Growth curve	Drug tested	Drug treatment regimen	TGI (%)	Model genetics
LU-01-0393	Lung cancer	Yes	Palbociclib LY2835219	60 mg/kg, QD 60 mg/kg, QD	83 89	CDK4, CDK6, CCND1 overexpression; p16 deletion; Rb1 positive
ES-06-0130	Esophageal Cancer	Yes	Palbociclib LY2835219	90 mg/kg, QD 90 mg/kg, QD	79 74	CCND1 overexpression; p16 deletion; Rb1 positive

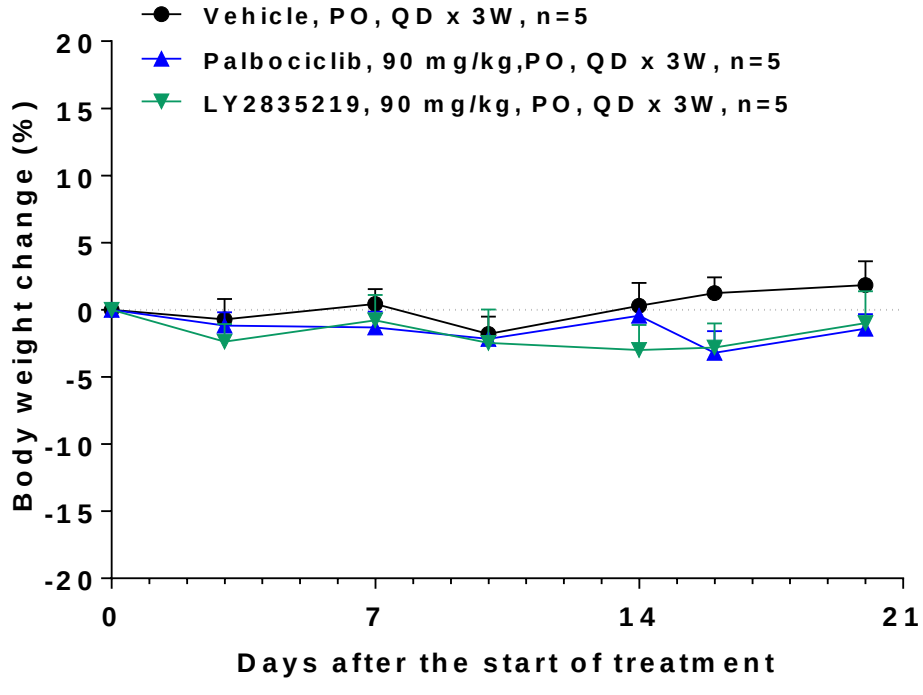
CDK4/6 inhibitors in LU-01-0393 lung cancer PDX model





CDK4/6 inhibitors in ES-06-0130 esophageal cancer PDX model





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