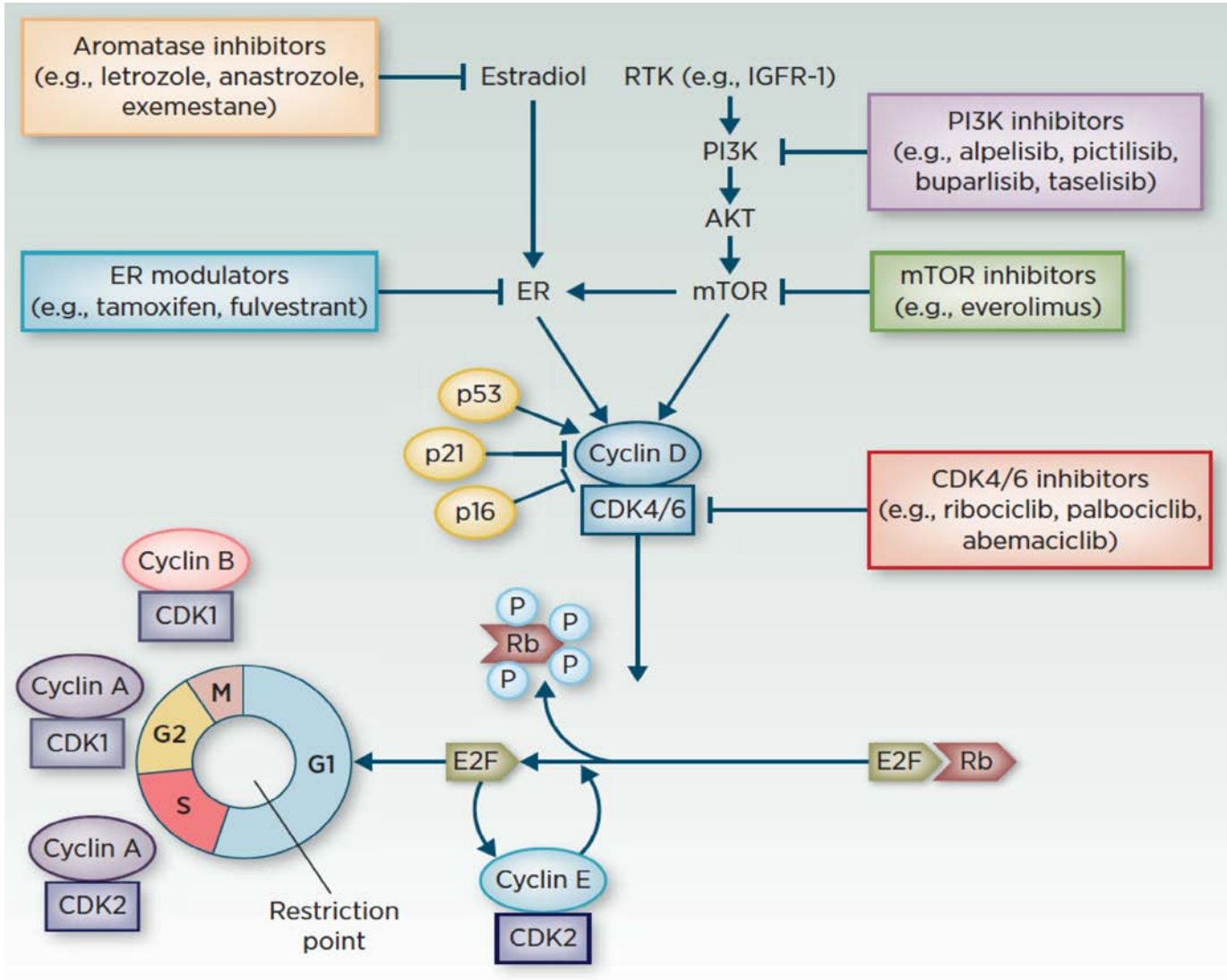
La farmacologia dei CDK4/6 inibitori

Romano Danesi

UO Farmacologia clinica e Farmacogenetica

Università di Pisa

The role of cyclin D–CDK4/6–p16–Rb pathway in the cell cycle



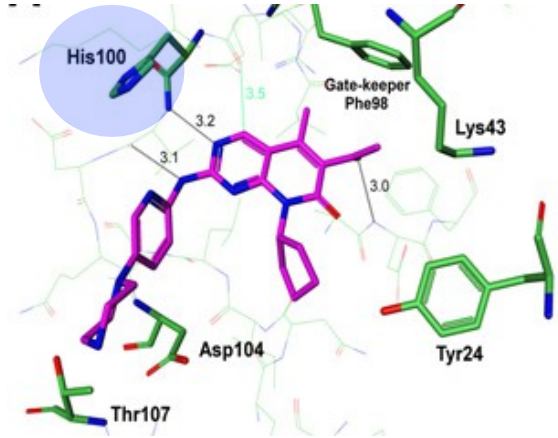
Debu Tripathy et al. Clin Cancer Res Published OnlineFirst March 28, 2017

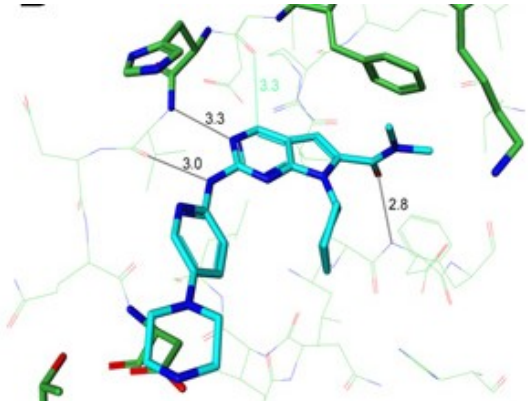
Classification of CDK inhibitors

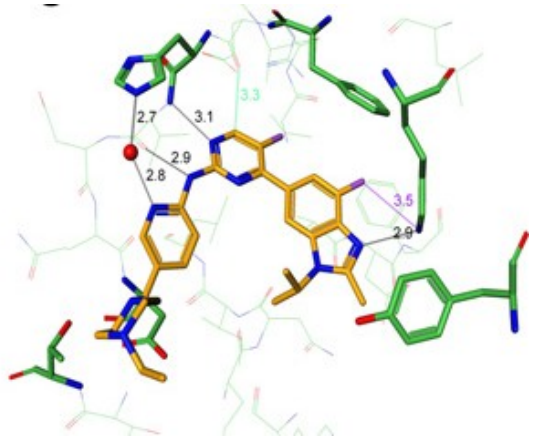
- **1st generation** (e.g., flavopiridol)
  - Low potency
  - Lack of specificity (pan-CDK) and off-target toxic effects
- **2nd generation** (e.g., dinaciclib)
  - Broad CDK family interactions
  - Equivalent potency for untransformed cells and tumor cells
- **3rd generation** (e.g., palbociclib)
  - Selective for a subset of the CDK kinase family
  - Selective for tumor cells compared to untransformed cells

Target interaction and pharmacodynamics of CDK4/6 inhibitors

Binding modes for 3rd generation drugs







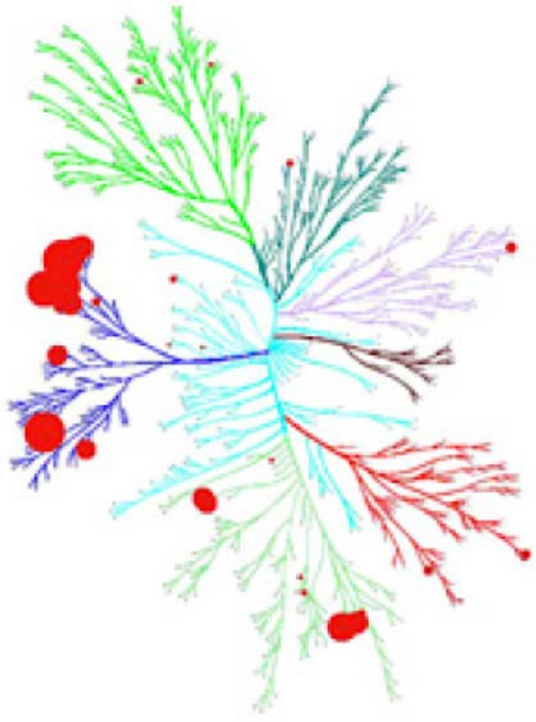
palbociclib
(PD-0332991)

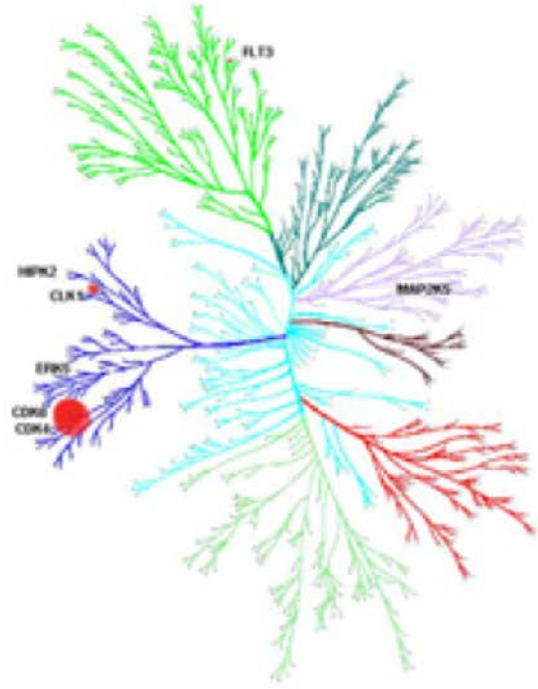
ribociclib
(LEE011)

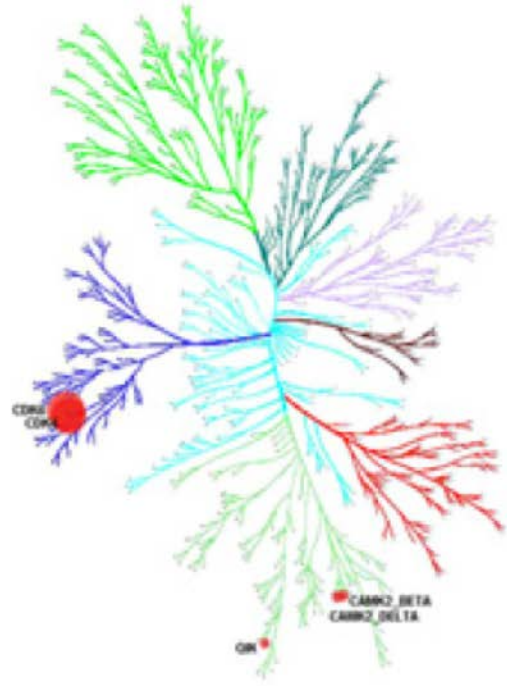
abemaciclib
(LY2835219)

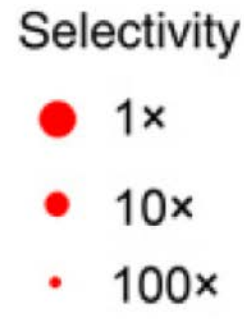
Ping Chen et al. Mol Cancer Ther 2016;15:2273-2281

Kinome selectivity of selective CDK4/6 inhibitors









Ping Chen et al. Mol Cancer Ther 2016;15:2273-2281

Biochemical and cellular potencies of selective CDK drugs

Analysis	Abemaciclib LY2835219	Palbociclib PD-0332991	Ribociclib LEE011
Biochemical			
CDK1/cyclinA_2 K_i (nmol/L)	330 ± 90	>1,400	>1,400
CDK2/cyclinE_1 K_i (nmol/L)	150 ± 60	>2,500	>2,500
CDK4/cyclinD_3 K_i (nmol/L)	0.07 ± 0.01	0.26 ± 0.03	0.53 ± 0.08
CDK5/p35 K_i (nmol/L)	86 ± 12	>2,000	>2,000
CDK6/cyclinD_1 K_i (nmol/L)	0.52 ± 0.17	0.26 ± 0.07	2.3 ± 0.3
CDK7/cyclinH/MAT1 K_i (nmol/L)	220 ± 10	>2,000	>2,000
CDK9/cyclinT_1 K_i (nmol/L)	4.1 ± 1.3	150 ± 10	190 ± 20

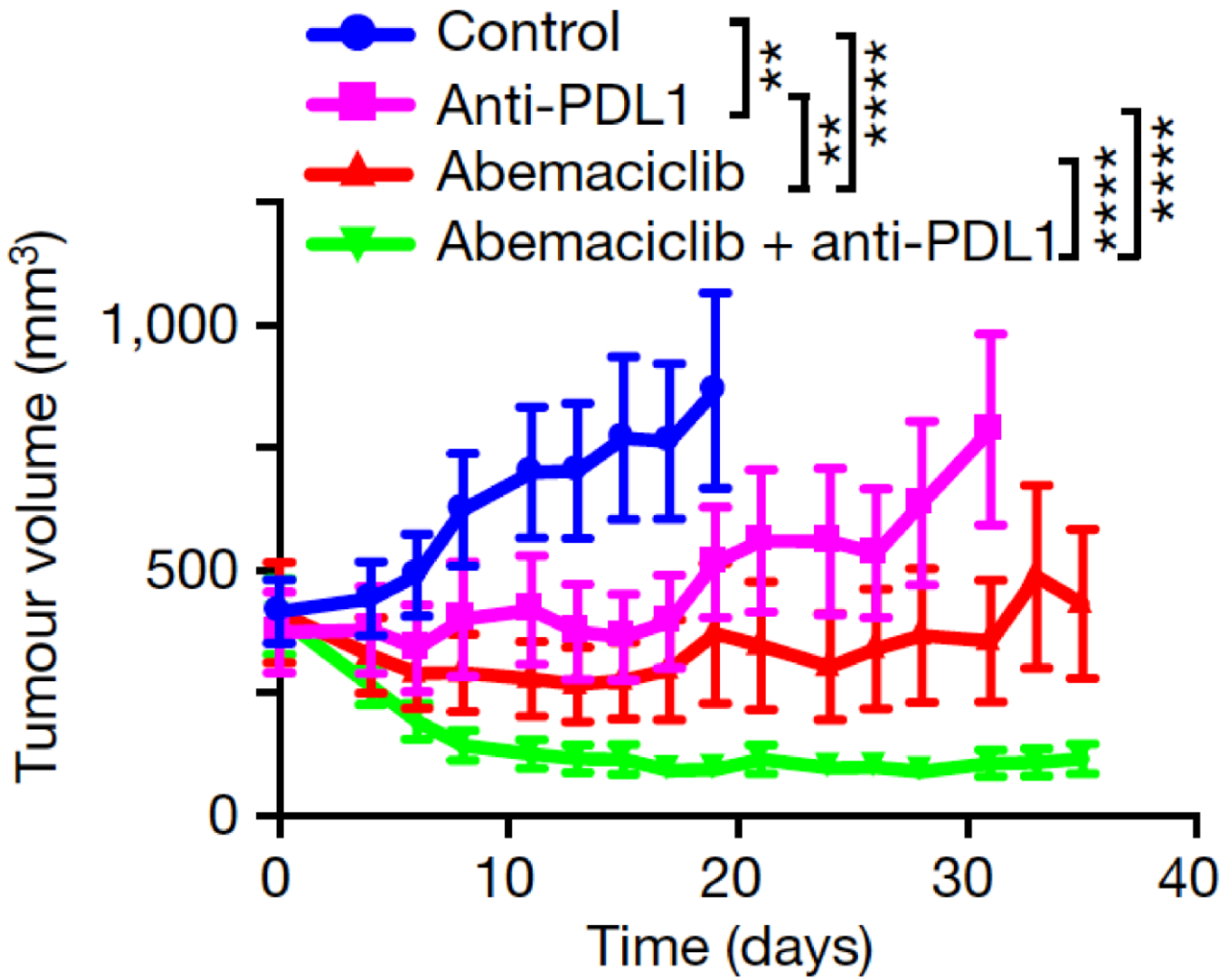
Biochemical and cellular potencies of selective CDK drugs

Analysis	Abemaciclib LY2835219	Palbociclib PD-0332991	Ribociclib LEE011
Cell proliferation			
Breast cancer (MCF-7) IC_{50} (nmol/L)	86 ± 14	120 ± 60	200 ± 90
Breast cancer (T47D) IC_{50} (nmol/L)	94 ± 41	130 ± 80	260 ± 130
Bone marrow mononuclear cells IC_{50} (nmol/L)	230 ± 27	240 ± 43	1,700 ± 231
Cytotoxicity			
Peripheral blood mononuclear cells IC_{50} (nmol/L)	4,700 ± 175	18,000 ± 521	>10,000

Ping Chen et al. Mol Cancer Ther 2016;15:2273-2281

CDK4/6 inhibition triggers anti-tumour immunity

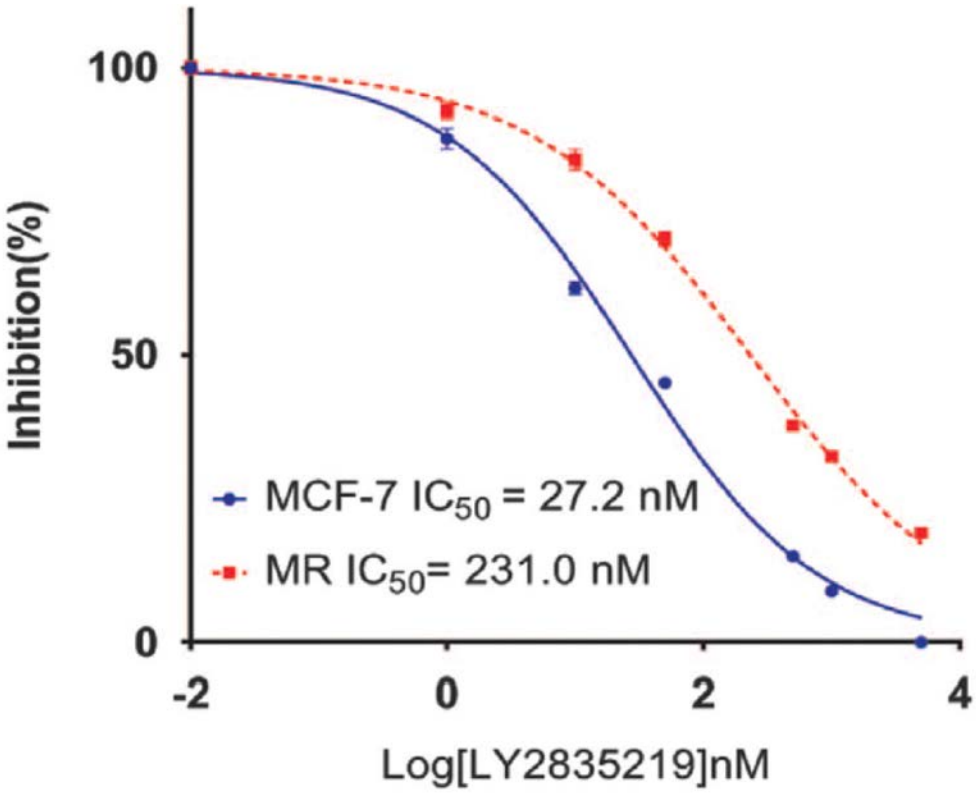
Tumor volume after treatment with abemaciclib with or without anti-PDL1

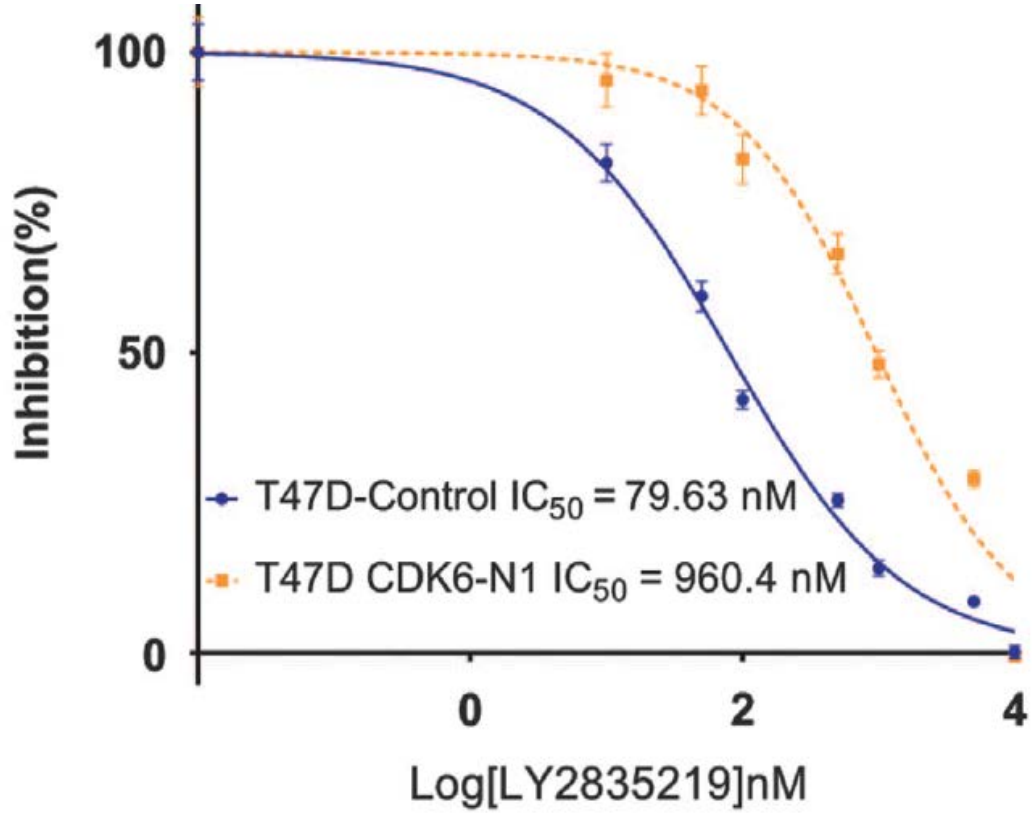


Shom Goel, et al. Nature, doi:10.1038/nature23465

Mechanisms of resistance

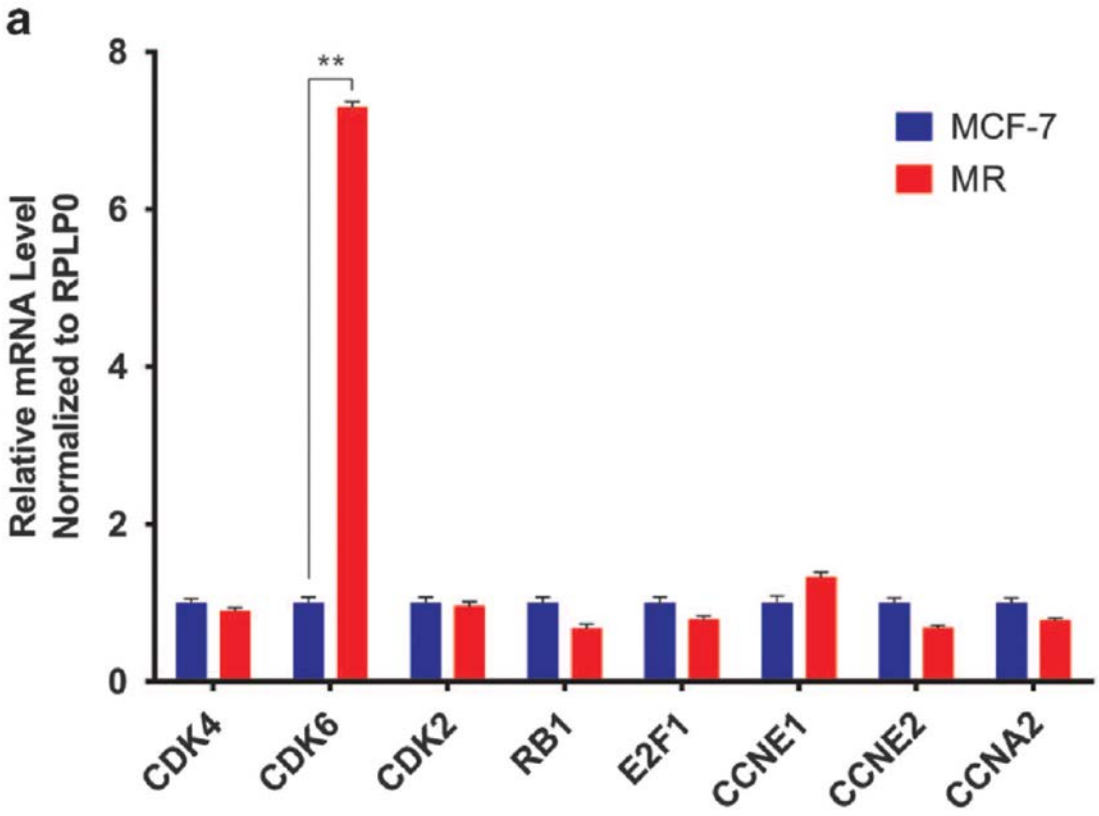
CDK6 amplification promotes BRCA resistance to CDK4/6i and loss of ER signaling

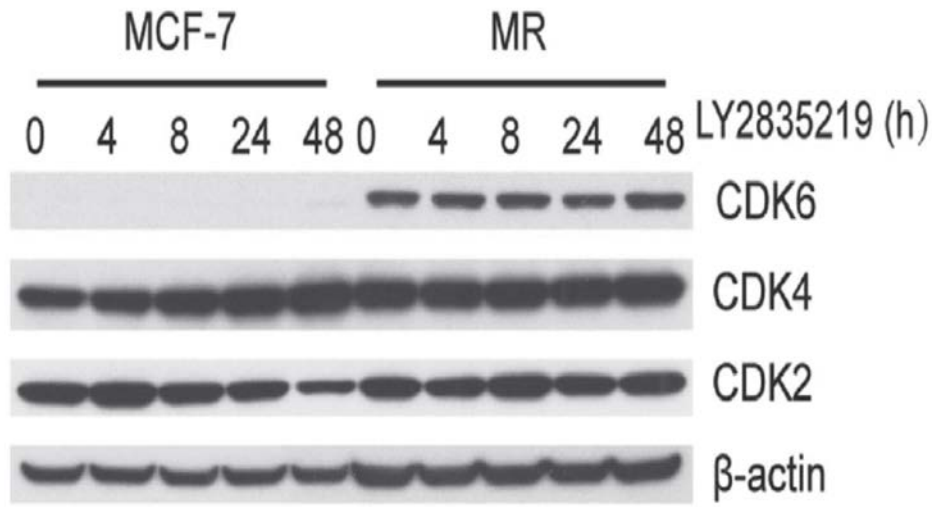




C Yang et al. Oncogene (2016), 1–10

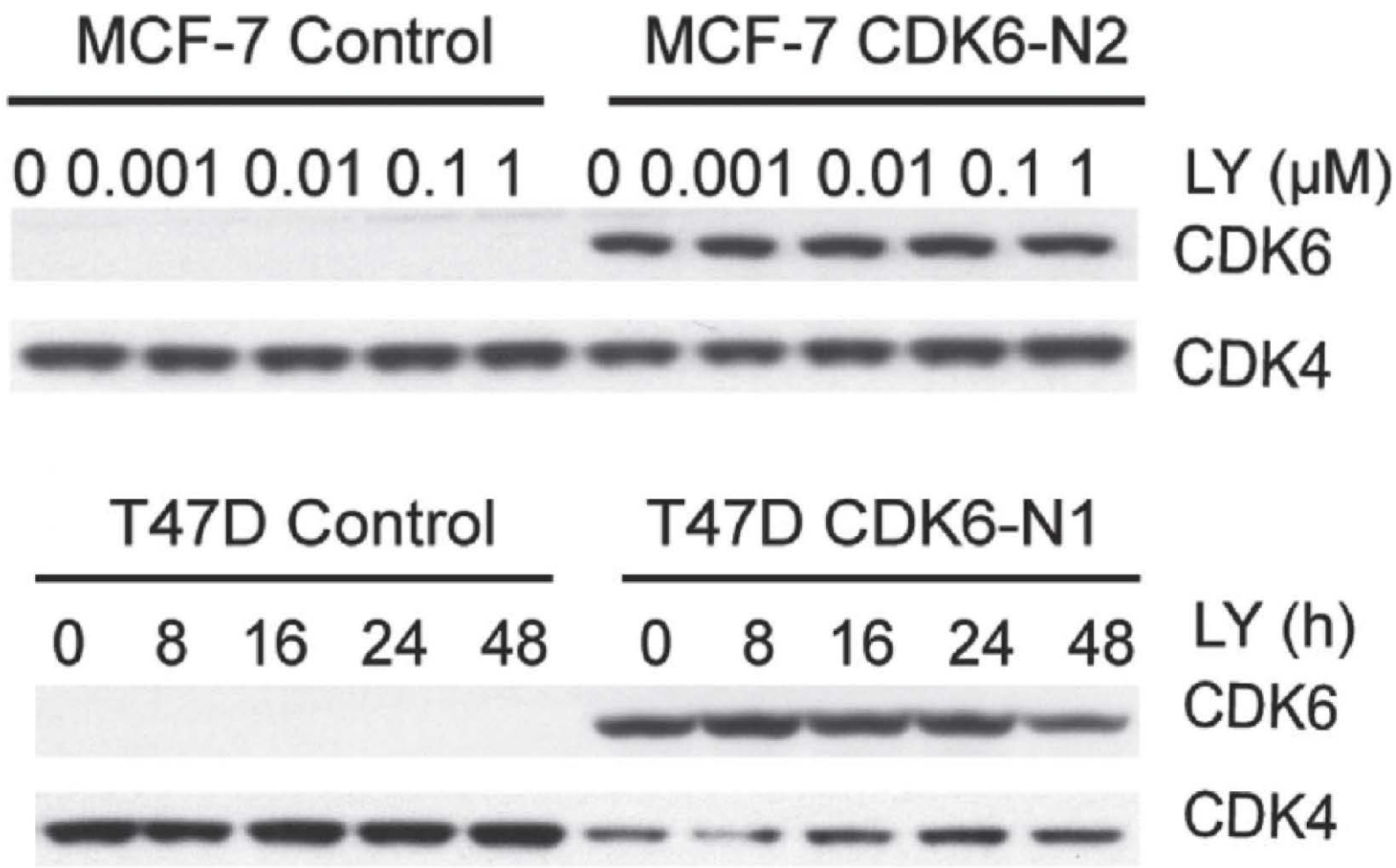
CDK6 amplification promotes BRCA resistance to CDK4/6 inhibitors





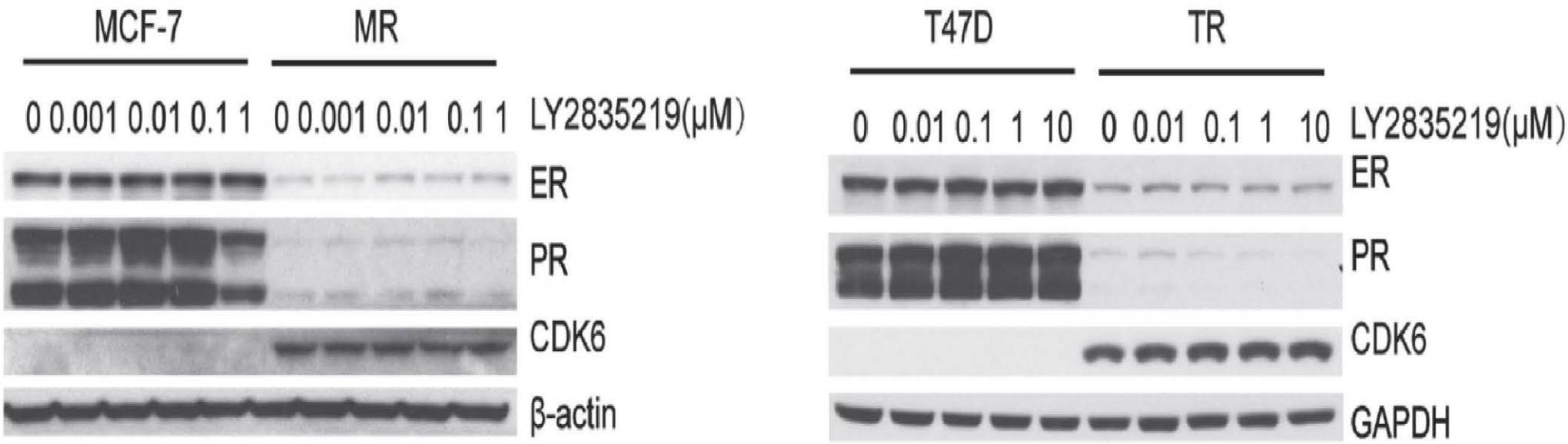
C Yang et al. Oncogene (2016), 1–10

CDK6 amplification promotes BRCA resistance to CDK4/6 inhibitors



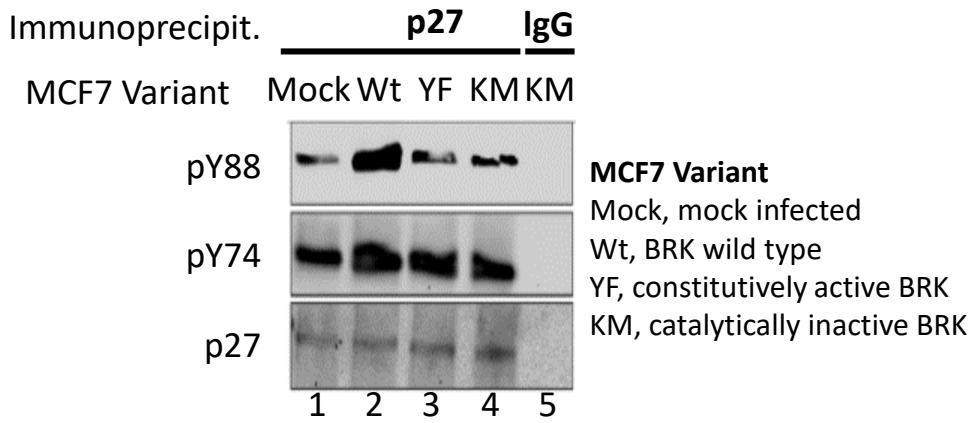
C Yang et al. Oncogene (2016), 1–10

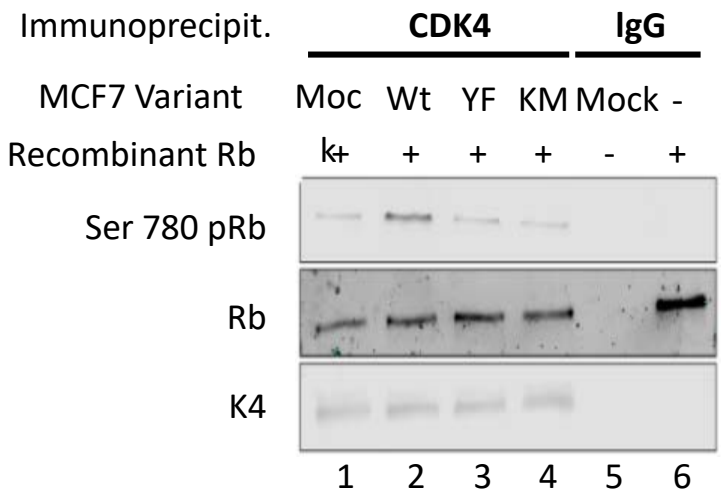
CDK6 amplification promotes BRCA resistance to CDK4/6i and loss of ER signaling

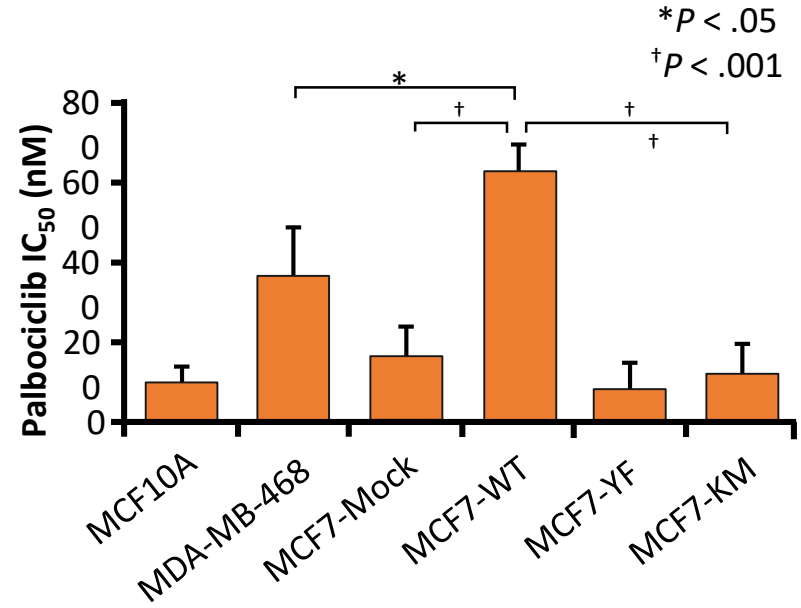


C Yang et al. Oncogene (2016), 1–10

Primary Resistance Possibly Linked to Breast Tumor–Related Kinase (BRK) Expression





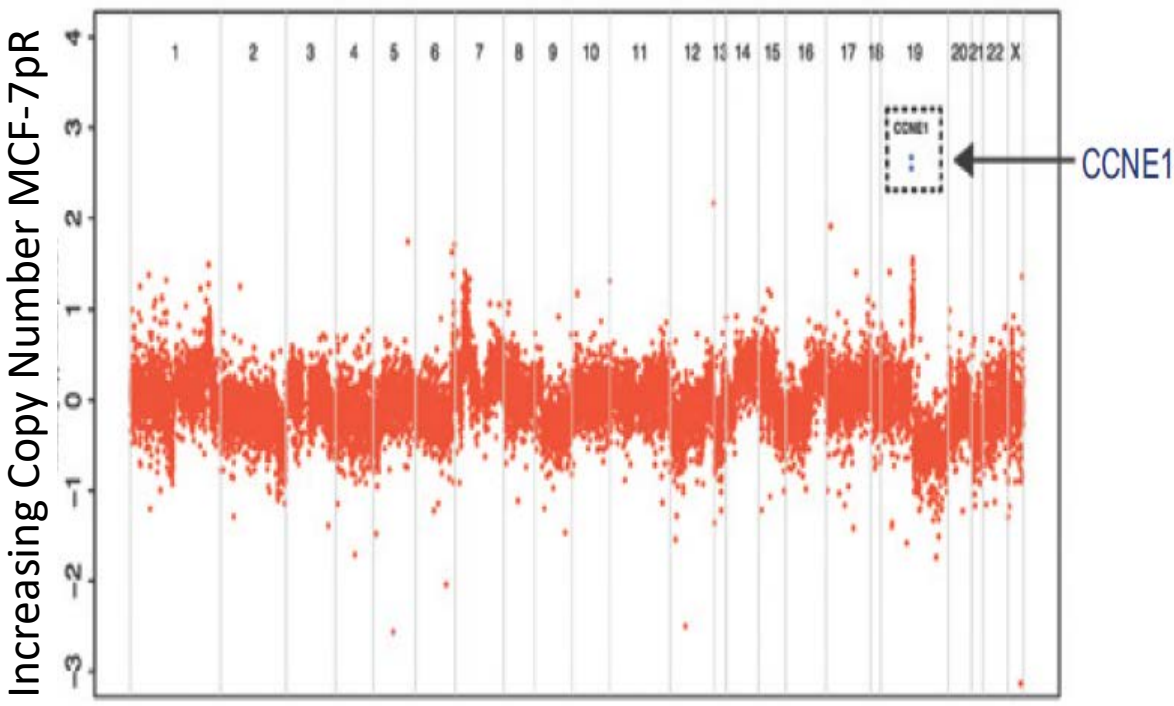


- BRK phosphorylates p27Kip1
- Results in activation of CDK4
- Leads to palbociclib resistance
- BRK has been shown to be overexpressed in breast carcinomas

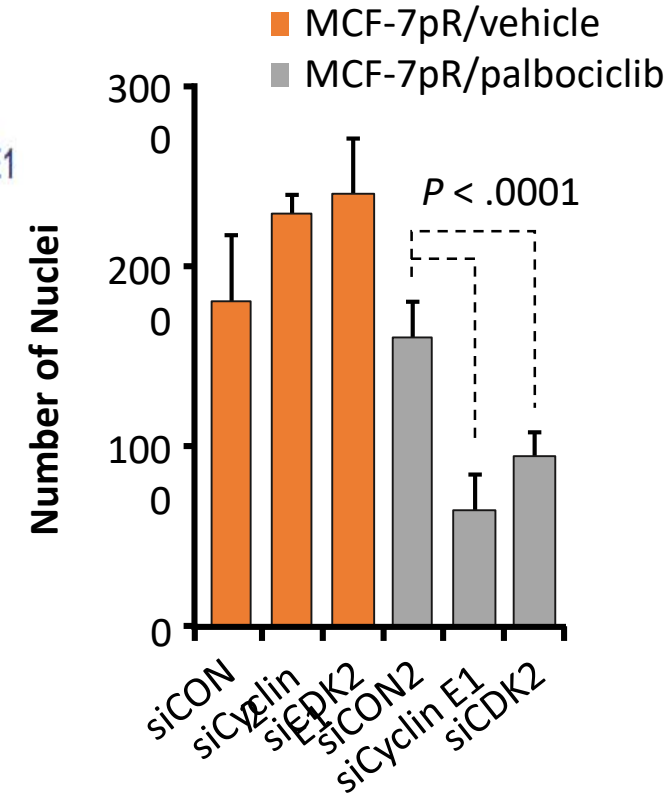
Patel P, et al. Mol Cell Biol. 2015;35:1506-1522.

Slide credit: clinicaloptions.com

Resistance to palbociclib and cyclin E1 gene amplification in a cell line model



Comparative gene copy number in MCF-7 parental and palbociclib-resistant cell lines



Herrera-Abreu MT, et al. Cancer Res. 2016;76:2301-2313.

Slide credit: clinicaloptions.com

Pharmacokinetics and drug interactions of CDK4/6 inhibitors

Selective CDK4/6 Inhibitors: Comparison of Key PK Characteristics

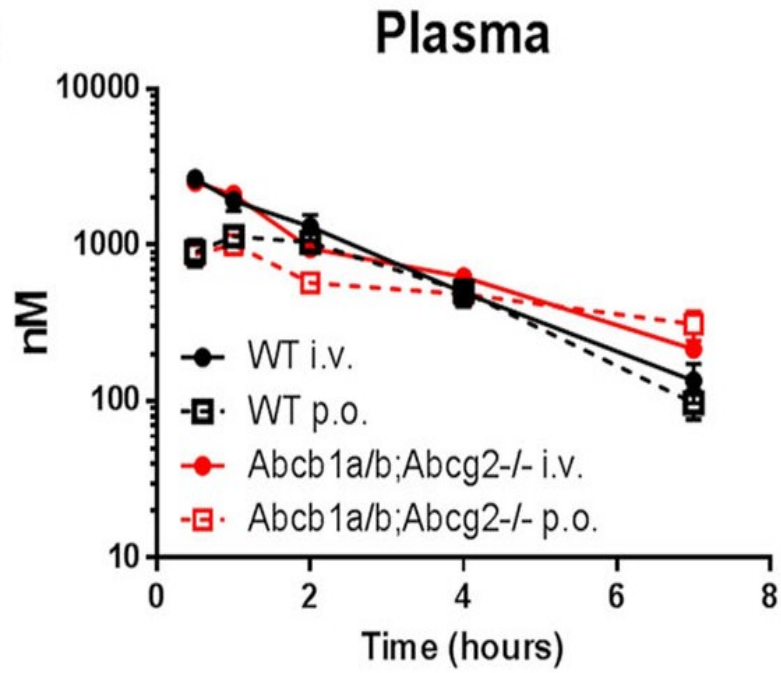
	Palbociclib	Ribociclib	Abemaciclib
Route	PO	PO	PO
Dose, mg	125 QD	600 QD	200 BID
Schedule	3 wks on/1 wk off	3 wks on/1 wk off	Continuous
Half-life, hrs	27.0	32.6	17.0-38.0
CNS penetration	No	No	Yes

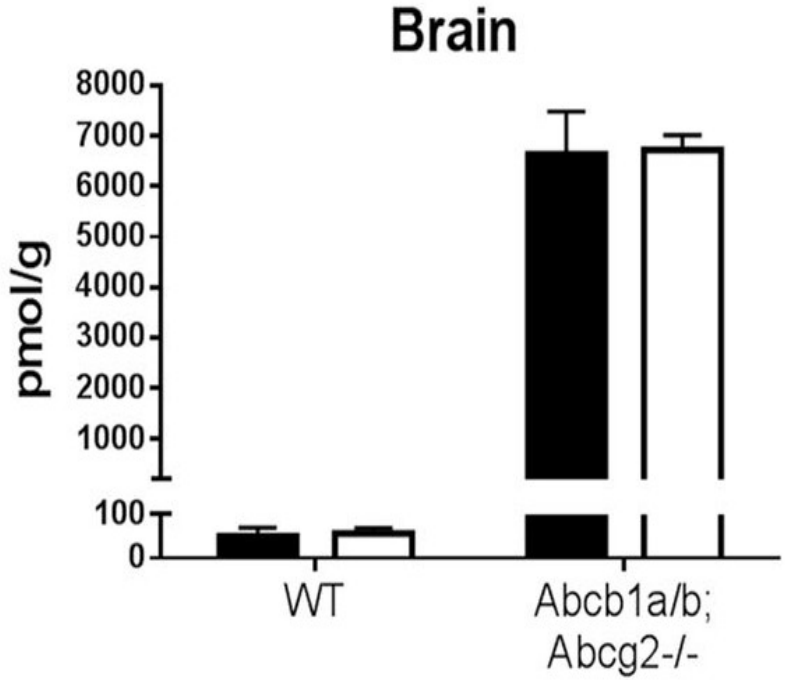
DeMichele A, et al. Clin Cancer Res. 2015;21:995-1001.
Hamilton E, et al. Cancer Treatment Rev. 2016;45:129-138.
Infante JR, et al. Clin Cancer Res. 2016;22:5696-5705.
Dickler MN, et al. ASCO 2016. Abstract 510.
Barroso-Sousa R, et al. Breast Care. 2016;11:167-173.

Slide credit: clinicaloptions.com

ABCB1 and ABCG2 restrict the brain penetration of palbociclib

- ABC transporter knockout mice





de Gooijer et al. Invest New Drugs (2015)

Potential drug-drug interactions

- Absorption and drug exposure were found to be low in the fasted state in a portion of the population, which was increased when administered with food. Therefore, taking palbociclib on an empty stomach could reduce drug levels and may compromise effectiveness in a subset of patients.
- Abemaciclib undergoes extensive hepatic metabolism in humans. CYP3A is the enzyme responsible for the majority of the CYP-mediated metabolism of abemaciclib and its metabolites. This suggests that concomitant use of strong CYP3A inducers or inhibitors should be avoided with abemaciclib.

Spring ML et al. TheOncologist 2017;22:1–10

Potential drug-drug interactions with palbociclib and ribociclib

Drug class	Agent	Treatment implications	Recommendation
Strong CYP3A inducers			
Antibiotics	All rifamycin class agents (e.g., rifampin, rifabutin, rifapentine)	Reduced exposure of palbociclib or ribociclib.	Avoid concomitant use and consider alternative therapy.
Anticonvulsants	Phenytoin, carbamazepine, barbiturates (e.g., phenobarbital)		
Other	Enzalutamide, St. John's Wort		

Spring ML et al. TheOncologist 2017;22:1–10

Potential drug-drug interactions with palbociclib and ribociclib

Strong CYP3A inhibitors			
Antibiotics	Clarithromycin, telithromycin	Increased exposure of palbociclib and ribociclib.	Avoid concomitant use and consider alternative therapy.
Antifungals	Itraconazole, ketoconazole, posaconazole, voriconazole		Reduce palbociclib dose to 75 mg or ribociclib dose to 400 mg once daily if patients must be coadministered a strong CYP3A inhibitor. Reinitiate previous palbociclib dose after 3–5 half-lives or ribociclib dose after 5 half-lives of inhibitor after discontinuation.
Antiretrovirals, protease inhibitors	Atazanavir, darunavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, telaprevir		
Other	Grapefruit or grapefruit juice, nefazodone		

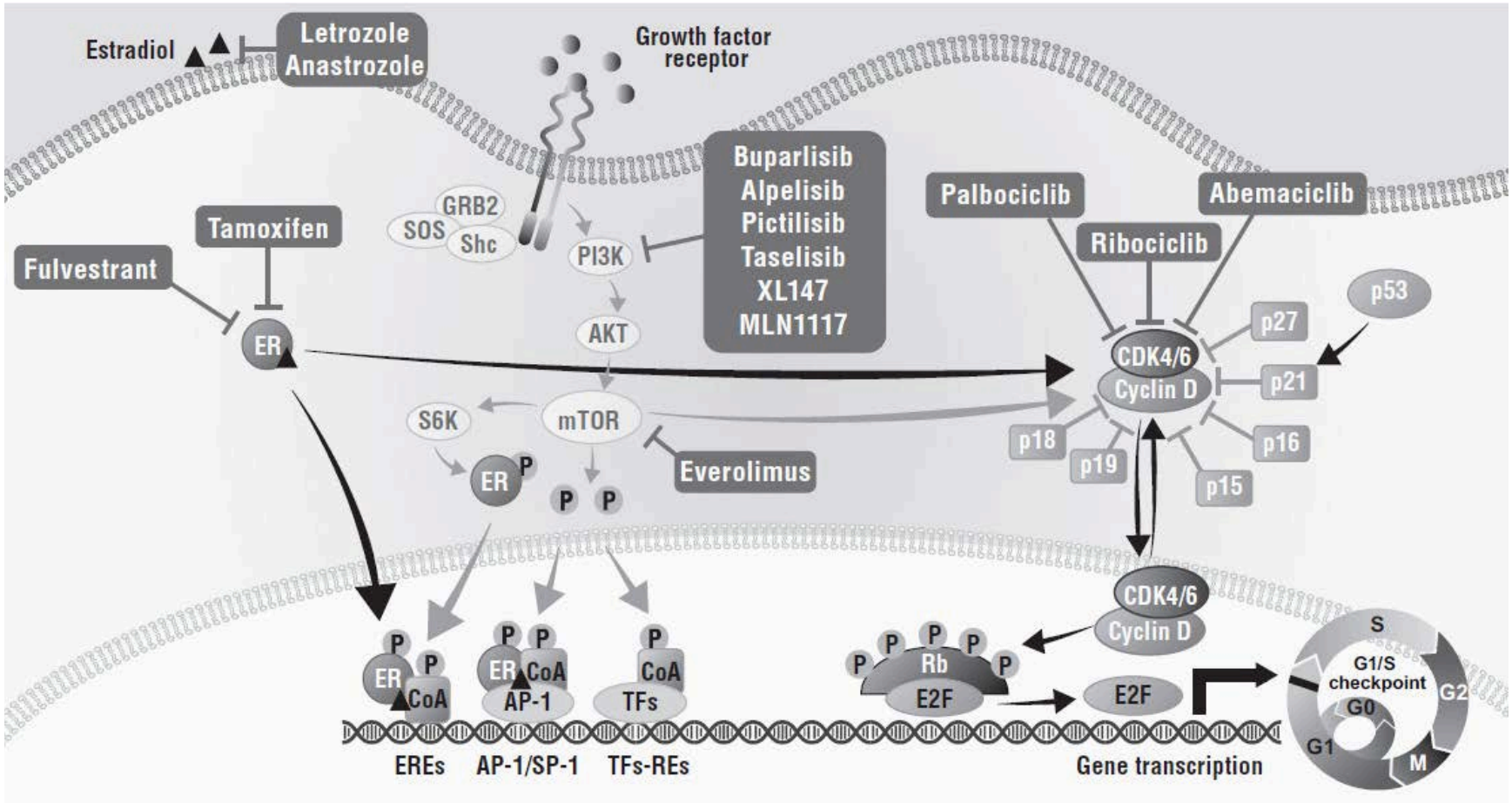
Spring ML et al. TheOncologist 2017;22:1–10

Potential drug-drug interactions with palbociclib and ribociclib

Sensitive CYP3A substrates with a narrow therapeutic index	Midazolam, alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus	May result in increased exposure of concomitant agent.	Monitor closely for signs of toxicity of concomitant agent. Dose of concomitant agent may need to be reduced.
For ribociclib only QT prolonging agents[a]			
Antiarrhythmics	Amiodarone, disopyramide, procainamide, quinidine, sotalol	QTc prolongation and related consequences.	Avoid coadministration with ribociclib
Other	Chloroquine, halofantrine, clarithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide, ondansetron (IV)		

Spring ML et al. TheOncologist 2017;22:1–10

Combo rationale



Spring L, et al. Discov Med. 2016 Jan;21(113):65-74.

Conclusive remarks

- Understanding of cell cycle and transcriptional effects of CDK4/6 inhibition is critical for clinical utilization
  - Combination with other targeted drugs
  - Optimal treatment sequence
- Interindividual variability needs to be monitored
  - Potential DDIs (TDM)
  - Genetic make up (pharmacogenetics)
- Translational research
  - Focus on mechanisms of resistance