

II EDIZIONE
BREAST
talk

27 MAGGIO
2021
ORE 15.00 - 18.00



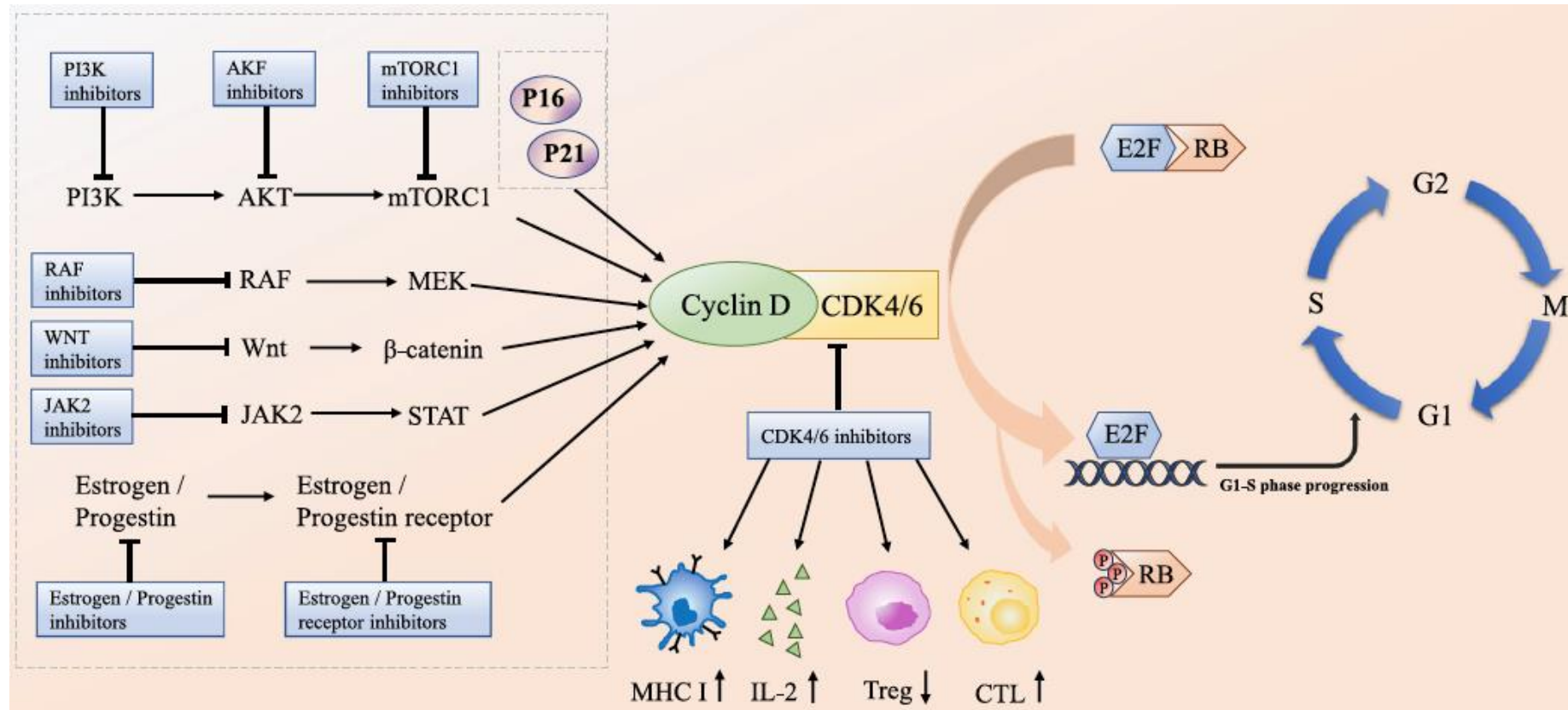
TITOLO: Principi di differenziazione farmacologica tra gli inibitori CDK4/6

RELATORE: Romano Danesi – Università' di Pisa

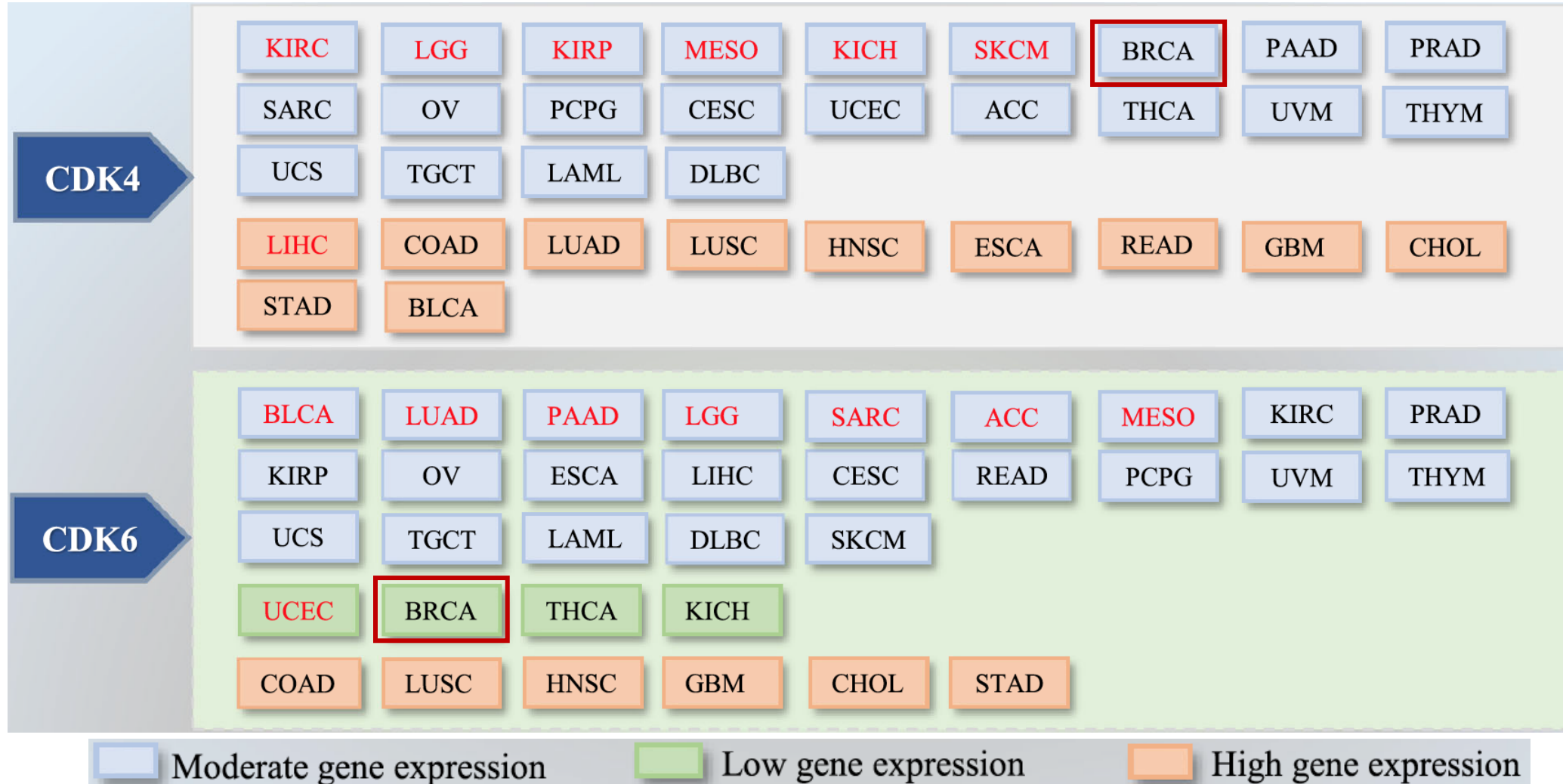
Classification of CDK inhibitors

- **1st generation** (e.g., alvocidib)
 - 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 and tumor cells
- **3rd generation** (e.g., palbociclib, ribociclib, abemaciclib)
 - Selective for a subset of the CDK kinase family
 - Selective for tumor compared to untransformed cells

Effects of CDK4/6i on cell cycle and immunity



Expression levels of CDK4/6 in various tumors



Differences among CDK4/6 inhibitors

	Alvocidib [NSC649890]	Abemaciclib [LY-2835219]	Palbociclib [PD-0332991]	Ribociclib [LEE011]
MW	401.84	506.59	447.54	434.55
CDK4/6 Inhibition	Reversible	Reversible	Reversible	Reversible
	IC50 Values			
CDK1	30 nM	> 1 μ M	> 10 μ M	> 100 μ M
CDK2	170 nM	> 500 nM	> 10 μ M	> 50 μ M
CDK4	100 nM	2 nM	9–11 nM	10 nM
CDK5	ND	ND	> 10 μ M	ND
CDK6	ND	5 nM	15 nM	39 nM
CDK7	\cong 300 nM	300 nM	ND	ND
CDK9	ND	57 nM	ND	ND
	Dose			
Daily dose	50–78 mg/m ² /d IV x 3d	150 mg orally, twice daily	125 mg orally, daily	600 mg orally, daily
	Pharmacokinetics			
Half-life [h]	11.6	17.4–38.1	26.7	32.6
Cmax [ng/mL]	109–134	249	78–194	1500
AUC [ng·hr/mL]	ND	4,280 (AUC ₀₋₂₄)	622–1599	22,000

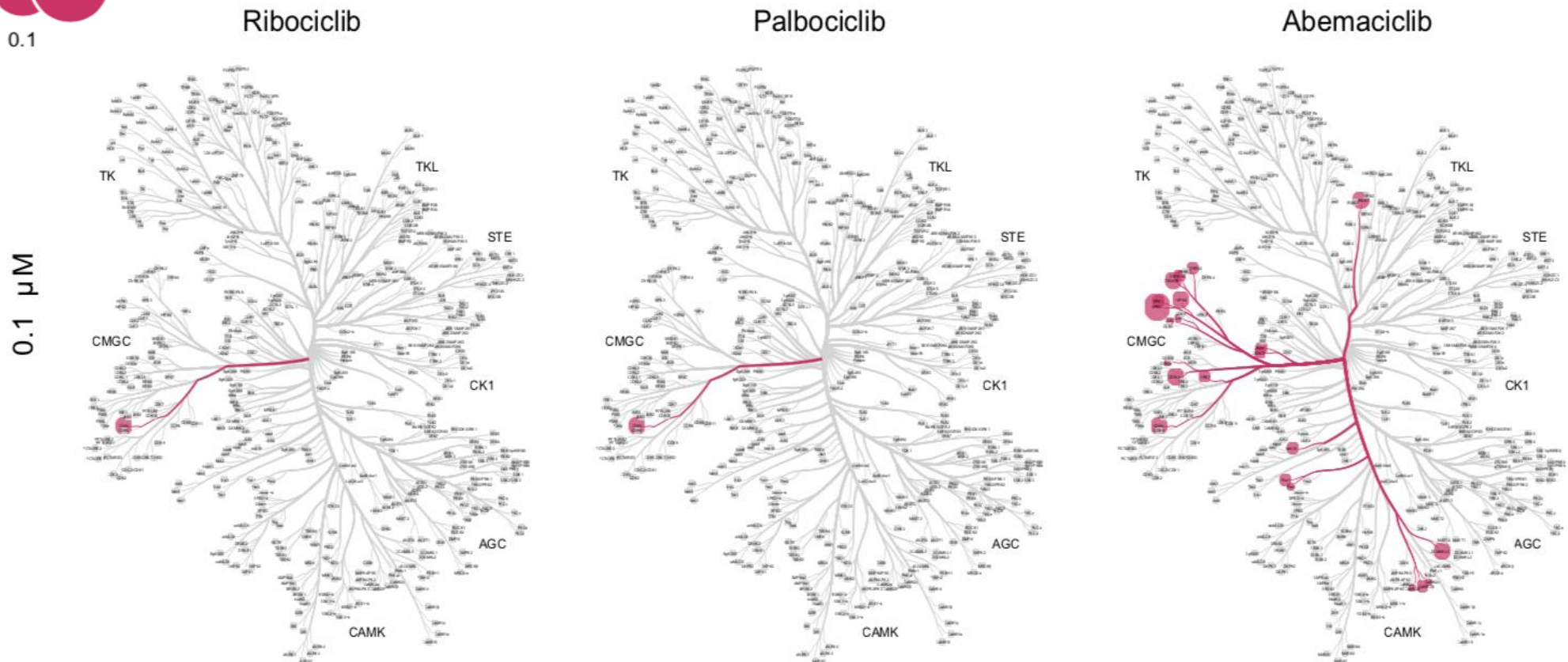
Kinome selectivity of CDK4/6i

Percent Remaining Activity

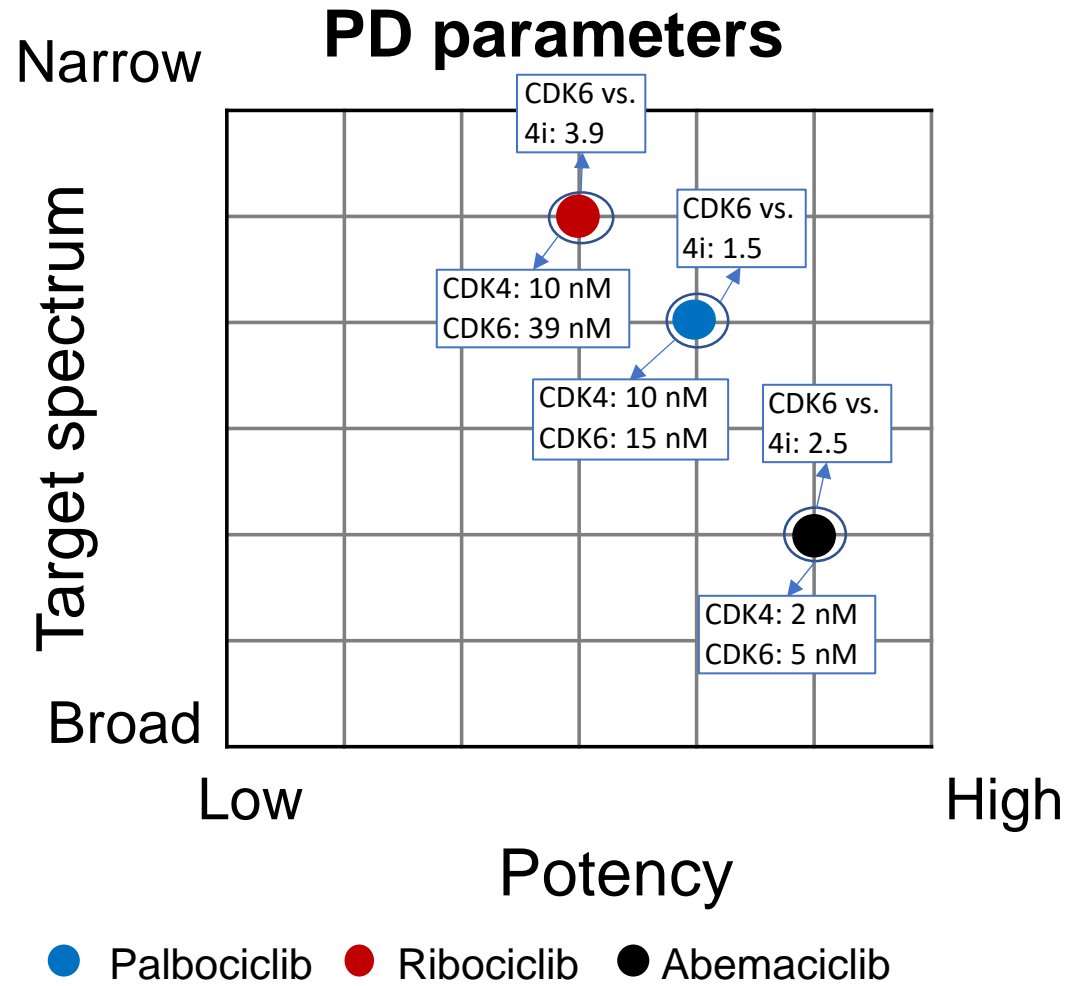
5-10 0.1-1 0



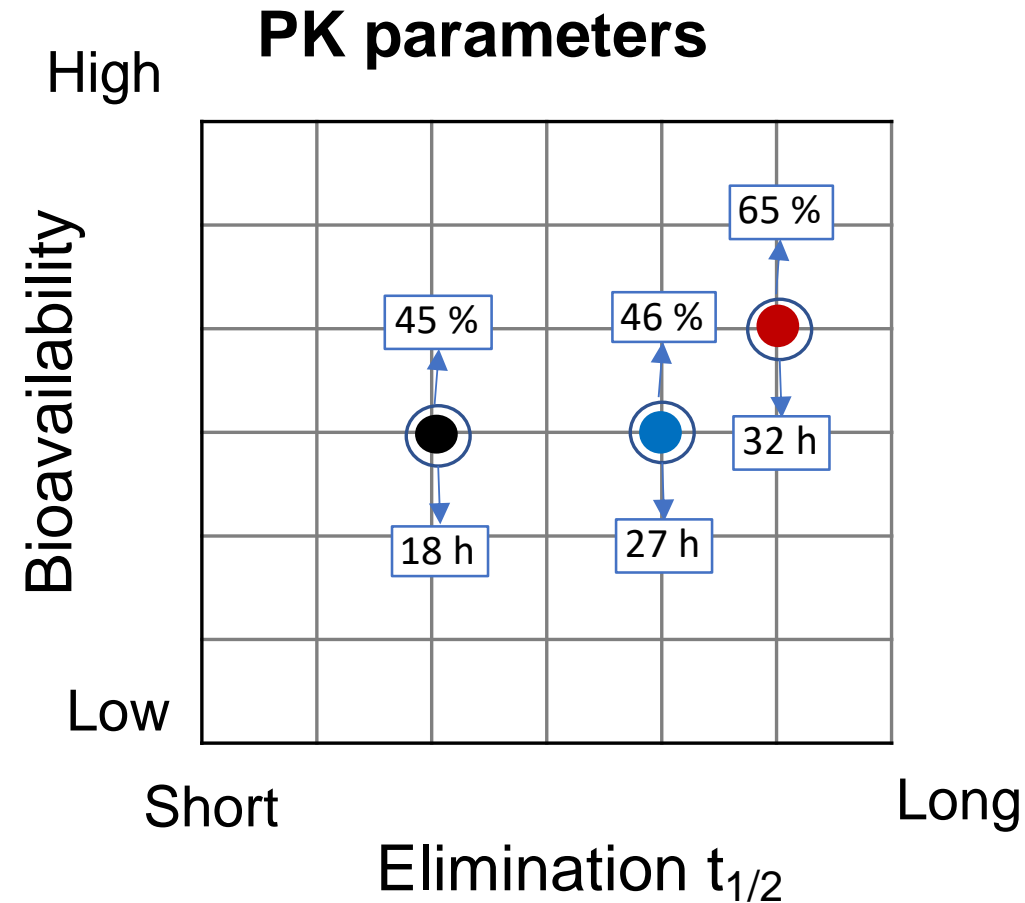
1-5 0.1



Pharmacologic differences of CDK4/6i

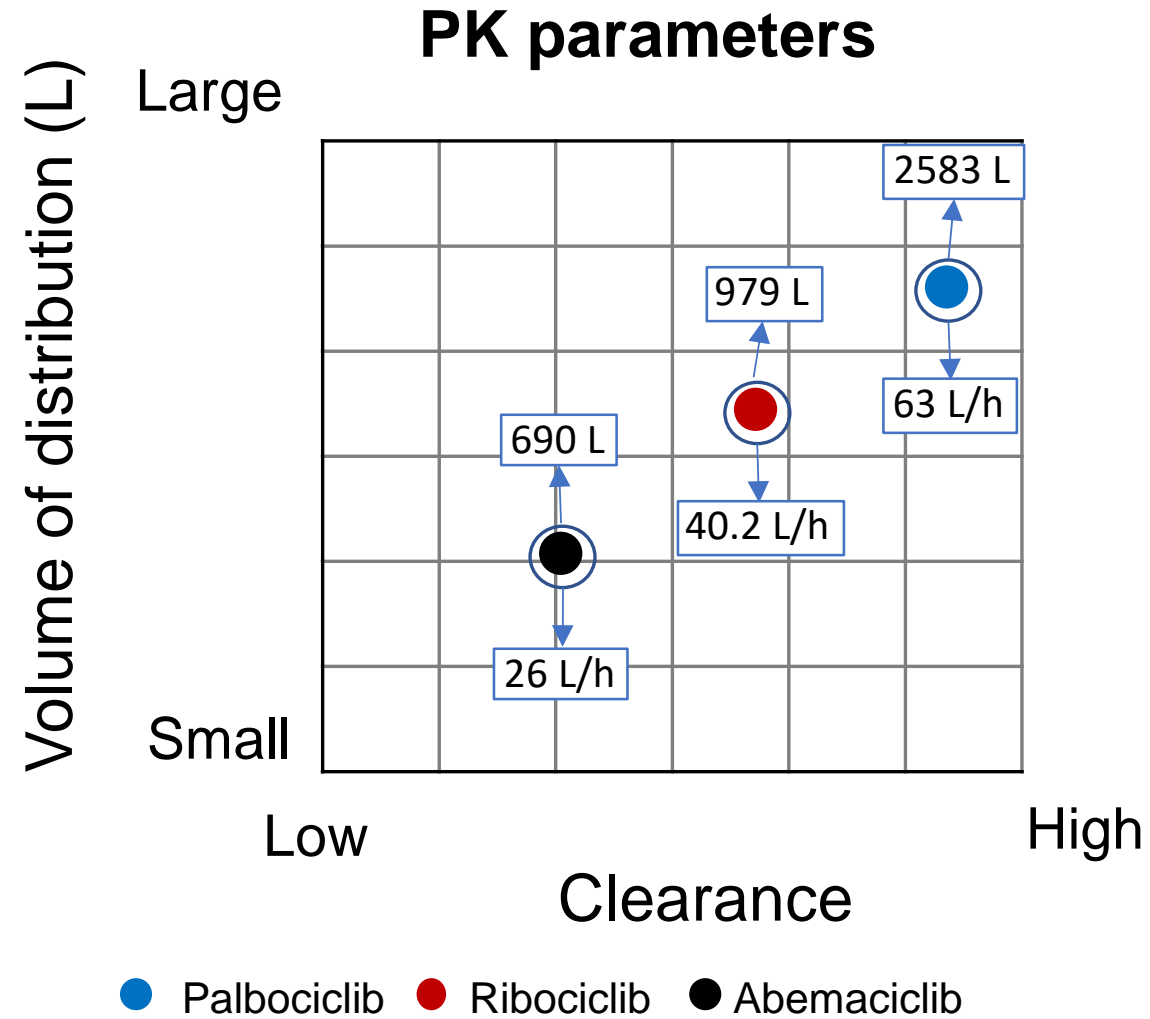


Pharmacologic differences of CDK4/6i



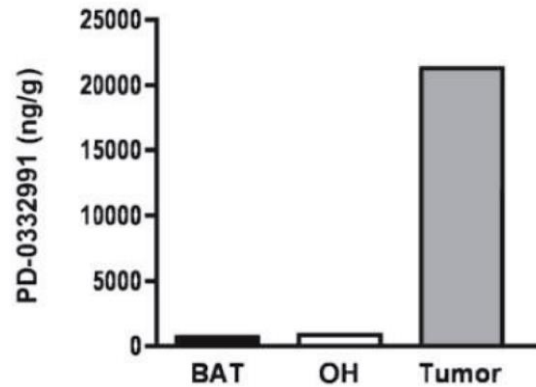
● Palbociclib ● Ribociclib ● Abemaciclib

Pharmacologic differences of CDK4/6i



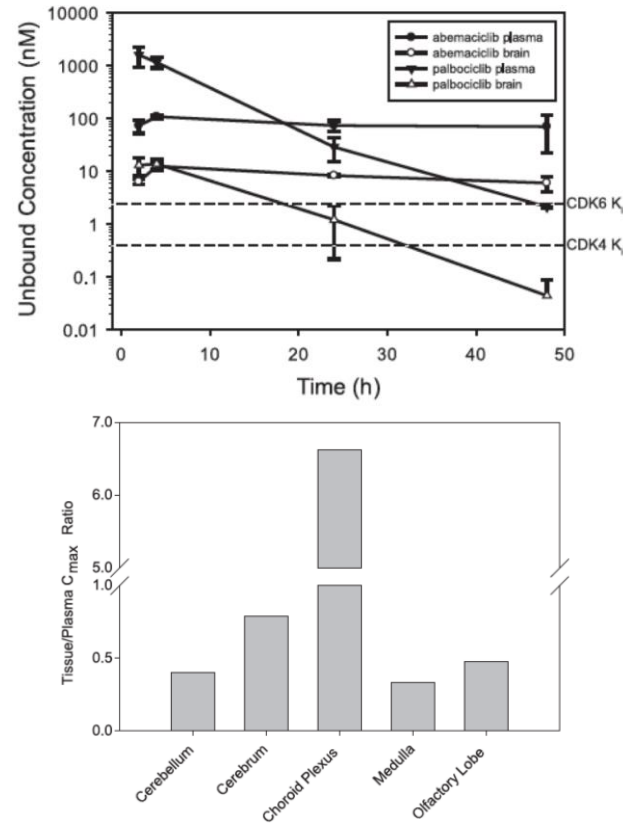
CDK4/6i and Blood Brain Barrier

Palbociclib levels in tumor, brain adjacent to tumor (BAT), and normal tissue from the opposite hemisphere (OH)



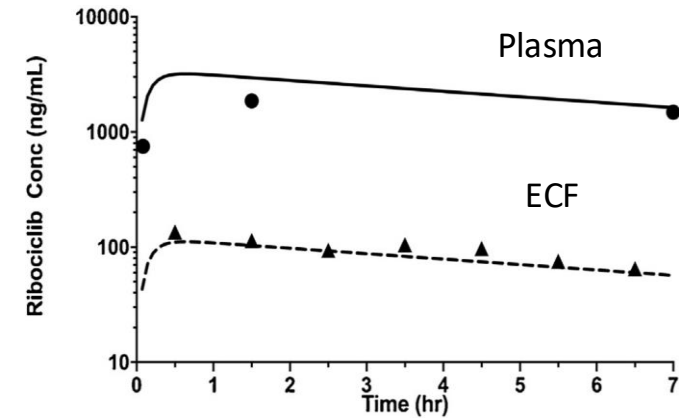
Michaud K et al. Cancer Res 2010;70:3228-3238

Distribution of **abemaciclib**-related radioactivity in brain tissues



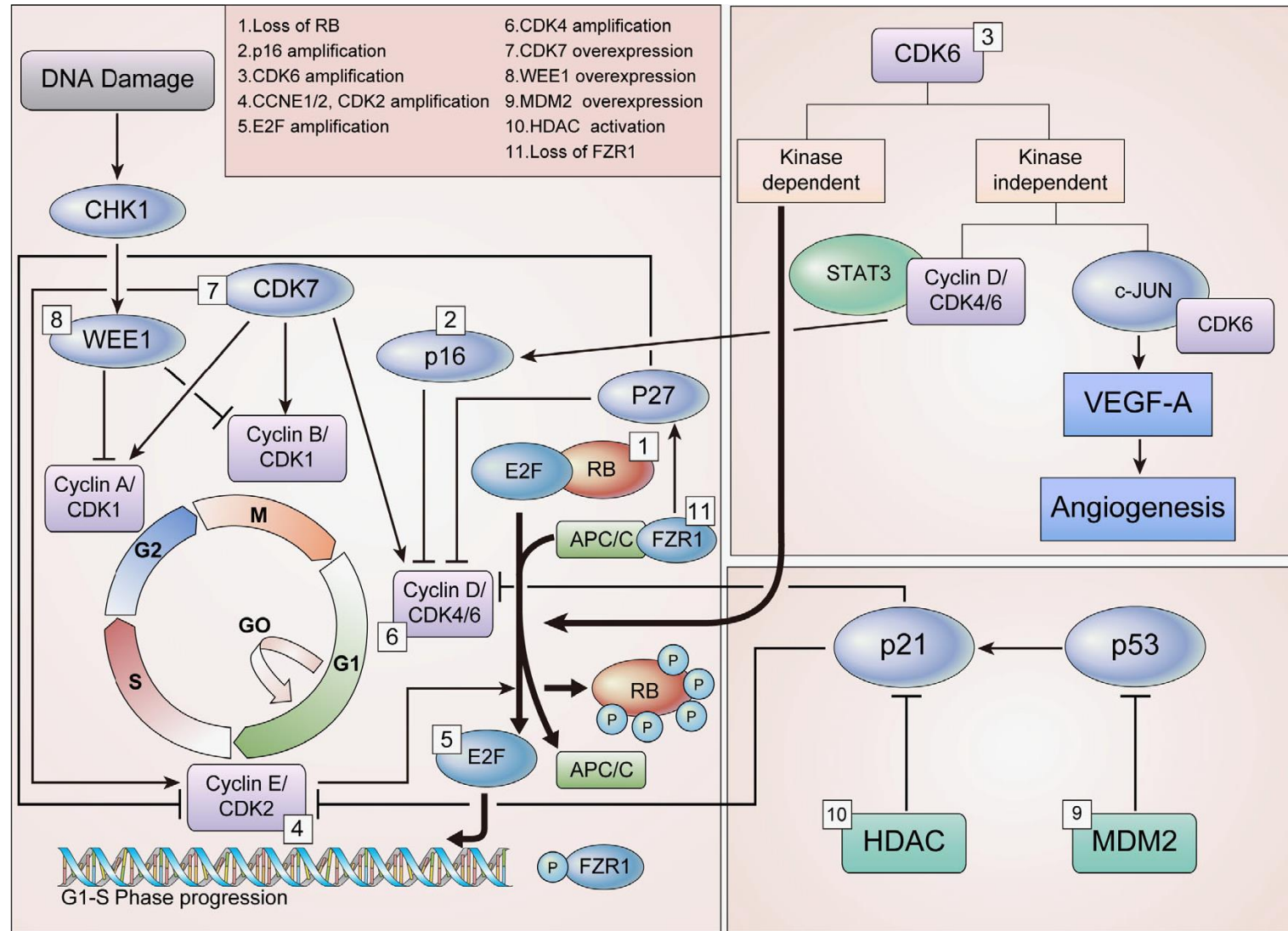
Raub TJ et al. Drug Metab Dispos 43:1360-1371, 2015

Ribociclib concentration time profile in plasma and brain extracellular fluid (ECF)

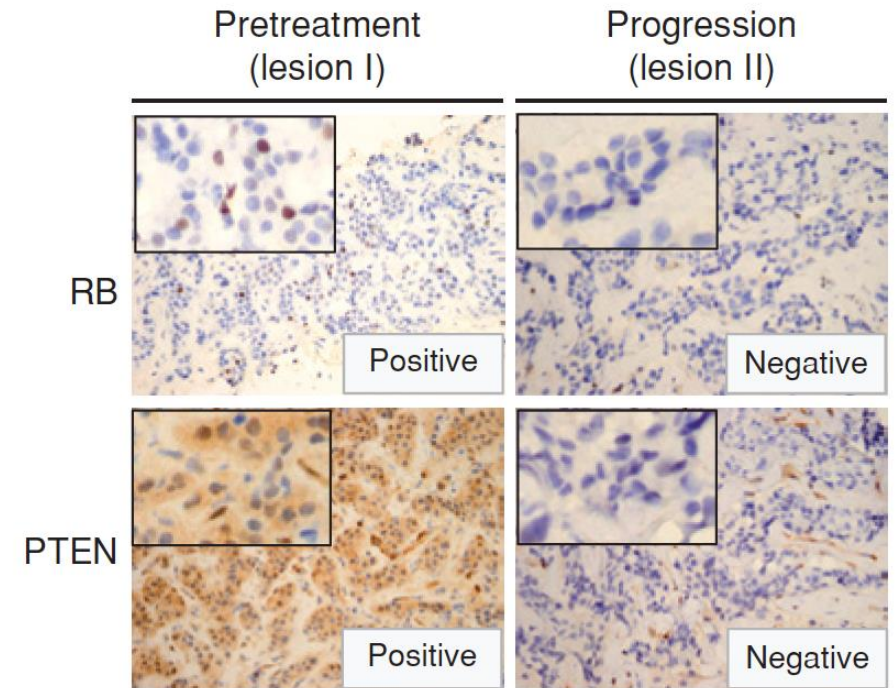
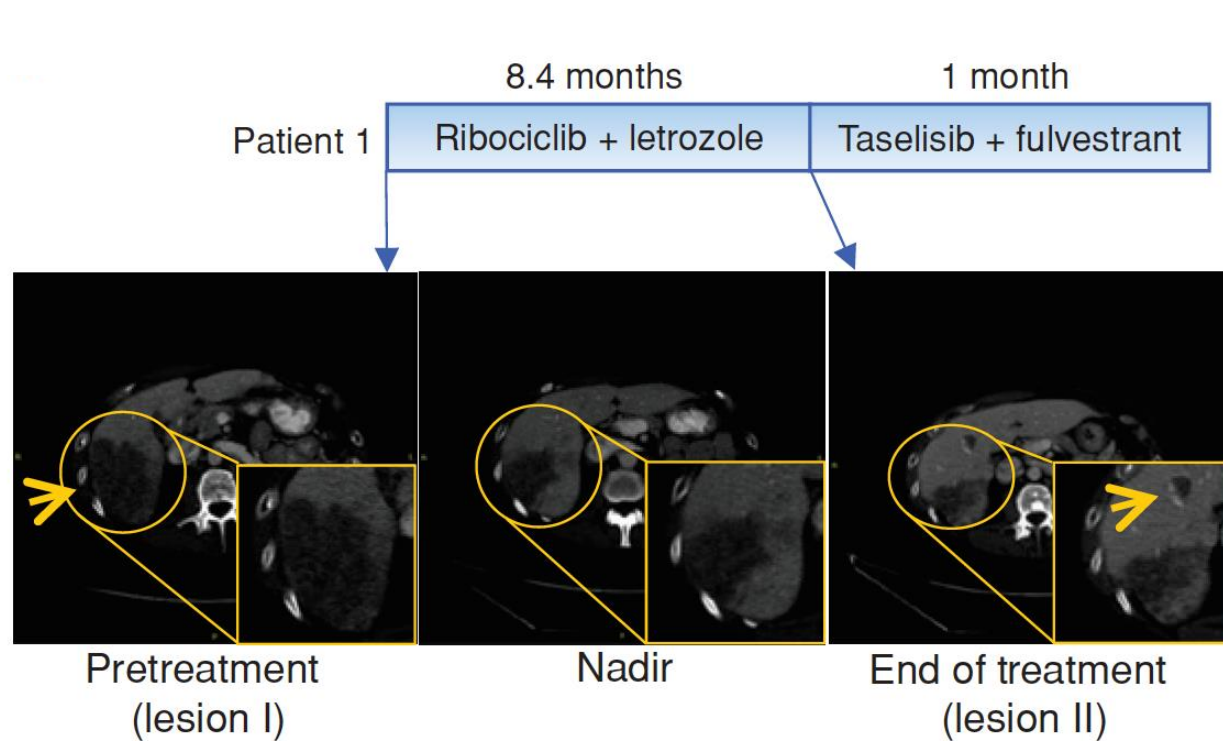


Kalantari et al. J Chromatogr B 2017;1057:110-117

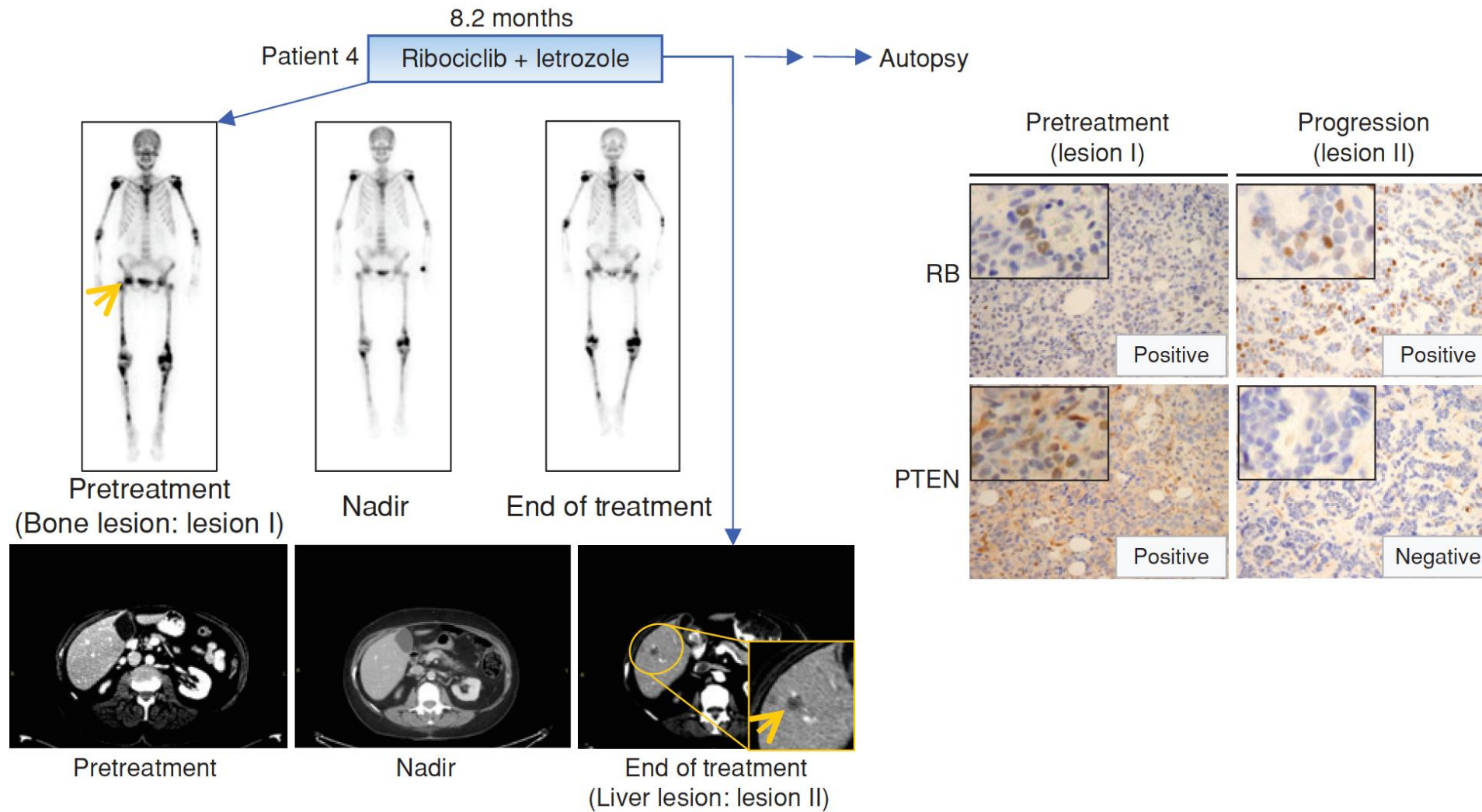
Cell cycle-specific mechanisms of CDK4/6i resistance



Loss of RB and PTEN in patients with acquired resistance to letrozole and CDKi



Loss of PTEN in patients with acquired resistance to CDKi



Conclusions

- Aberrations of CDK4/6 or CDKN2A/B are common in various cancer types being second in frequency to only p53 mutations.
- CDK4/6 or CDKN2A/B aberrations are associated with poor overall survival.
- The biologic role of CDK4/6 provides a strong rationale for targeting the cyclin kinase pathway in cancer.
- There is compelling evidence of pharmacological differences among CDK4/6i