II EDIZIONE

BREAST talk

27 MAGGIO
2021
ORE 15.00 - 18.00

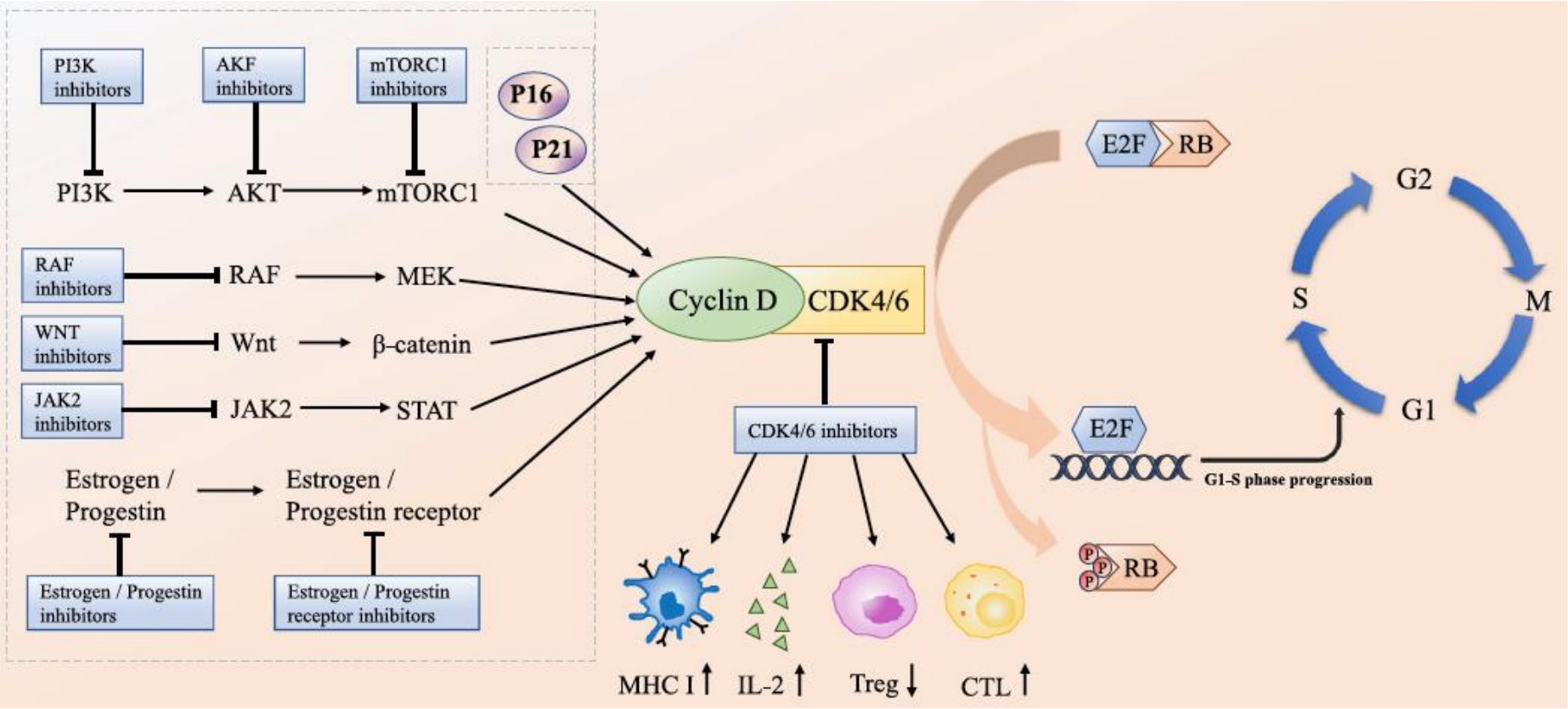
TITOLO: Principi di differenziazione farmacologi tra gli inibitori CDK4/6

RELATORE: Romano Danesi – Universita' di Pisa

Classification of CDK inhibitors

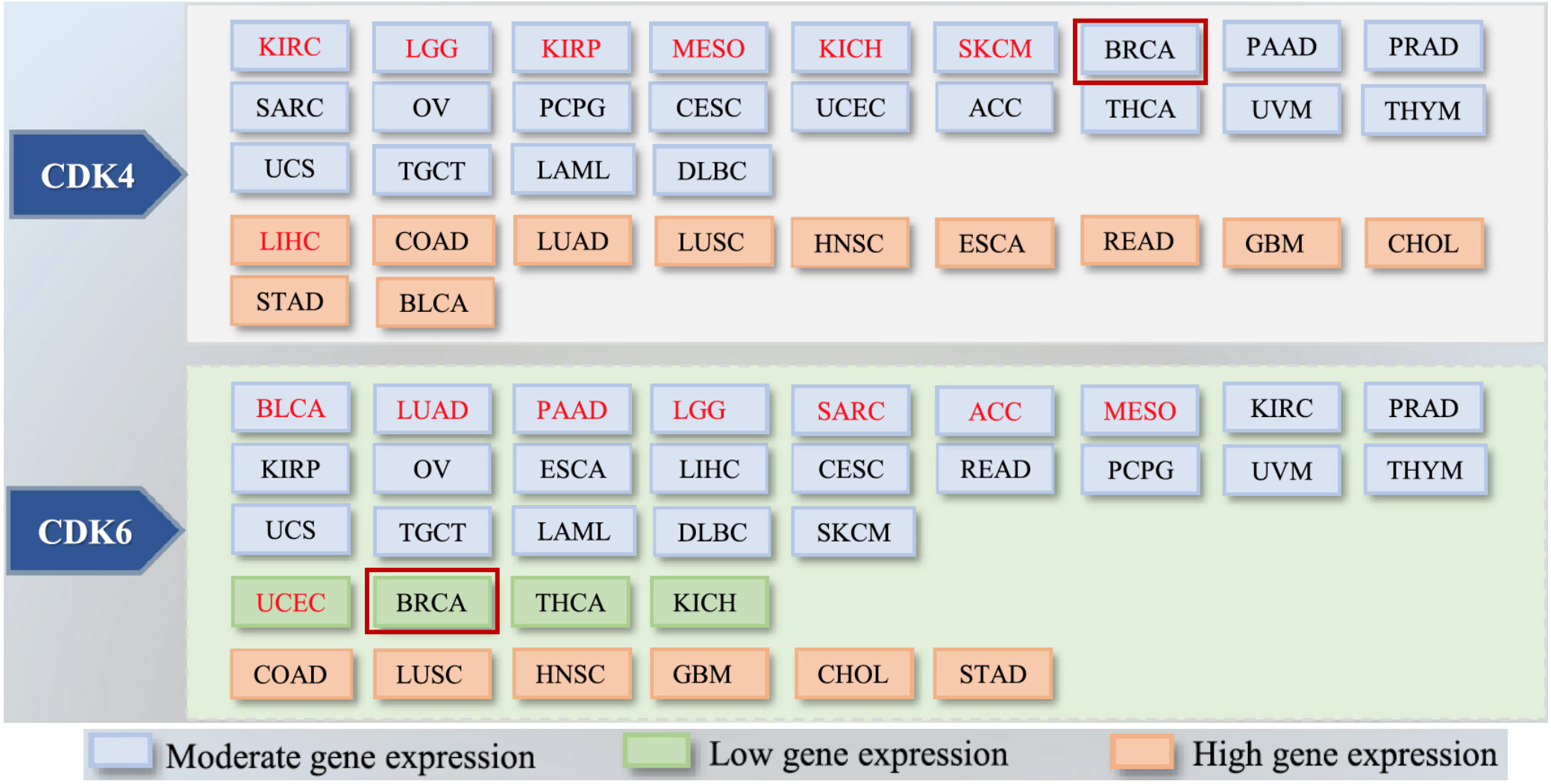
- **1st generation** (e.g., alvocidib)
  - Low potency
  - Lack of specificity (pan-CDK) and off-target toxic effects
- **2nd generation** (e.g., dinaciclib)
  - Broad CDK family interactions
  - Equivalent potency for untransformed and tumor cells
- **3rd generation** (e.g., palbociclib, ribociclib, 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



Du et al. Journal of Hematology & Oncology (2020) 13:41

Expression levels of CDK4/6 in various tumors



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Differences among CDK4/6 inhibitors

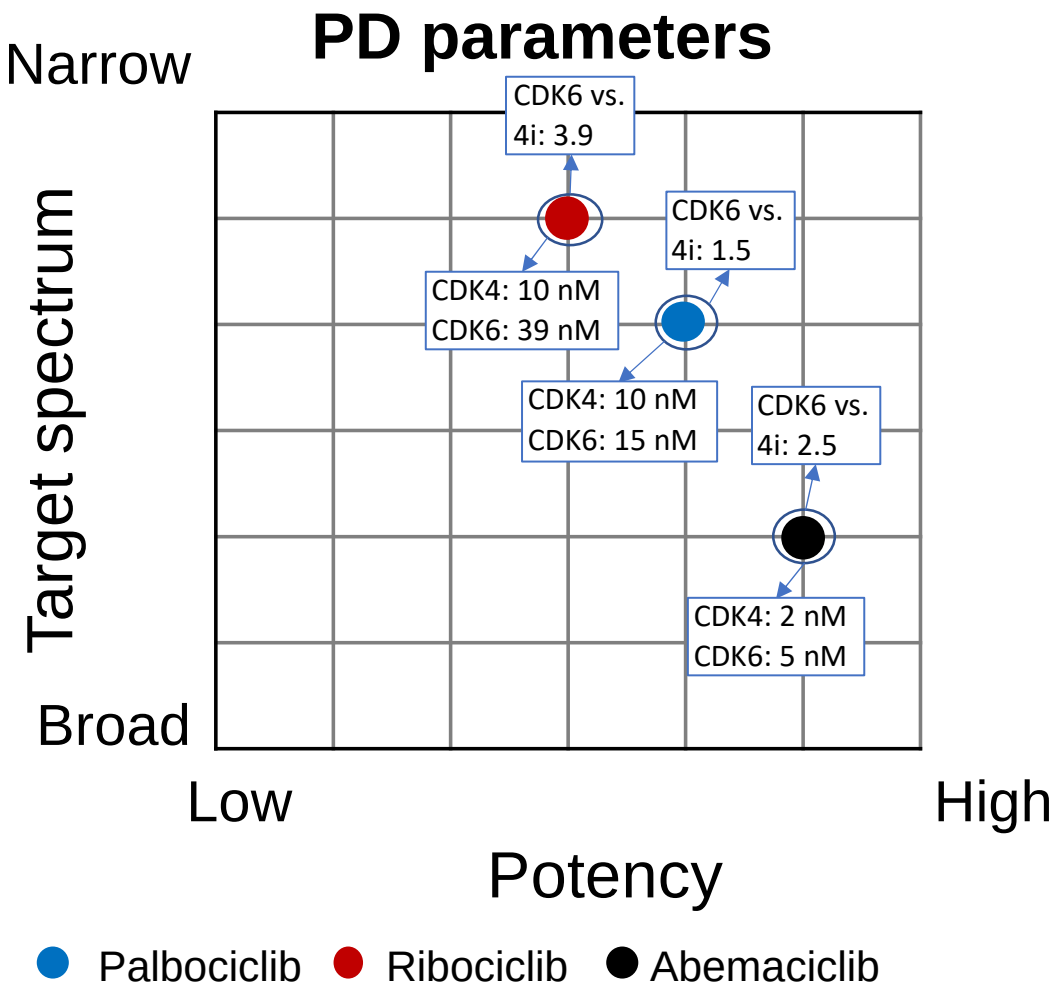
	Alvocidib [NSC649890]	Abemaciclib [LY-2835219]	Palbociclib [PD-0332991]	Ribociclib [LEE011]
MW	401.84	506.59	447.54	434.55
CDK4/6 Inhibition	Reversible	Reversible	Reversible	Reversible
		IC50 Values		
CDK1	30 nM	> 1 μM	> 10 μM	> 100 μM
CDK2	170 nM	> 500 nM	> 10 μM	> 50 μM
CDK4	100 nM	2 nM	9–11 nM	10 nM
CDK5	ND	ND	> 10 μM	ND
CDK6	ND	5 nM	15 nM	39 nM
CDK7	≅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

Laderian B, Fojo T. Semin Oncol 2017;44:395–403

Kinome selectivity of CDK4/6i

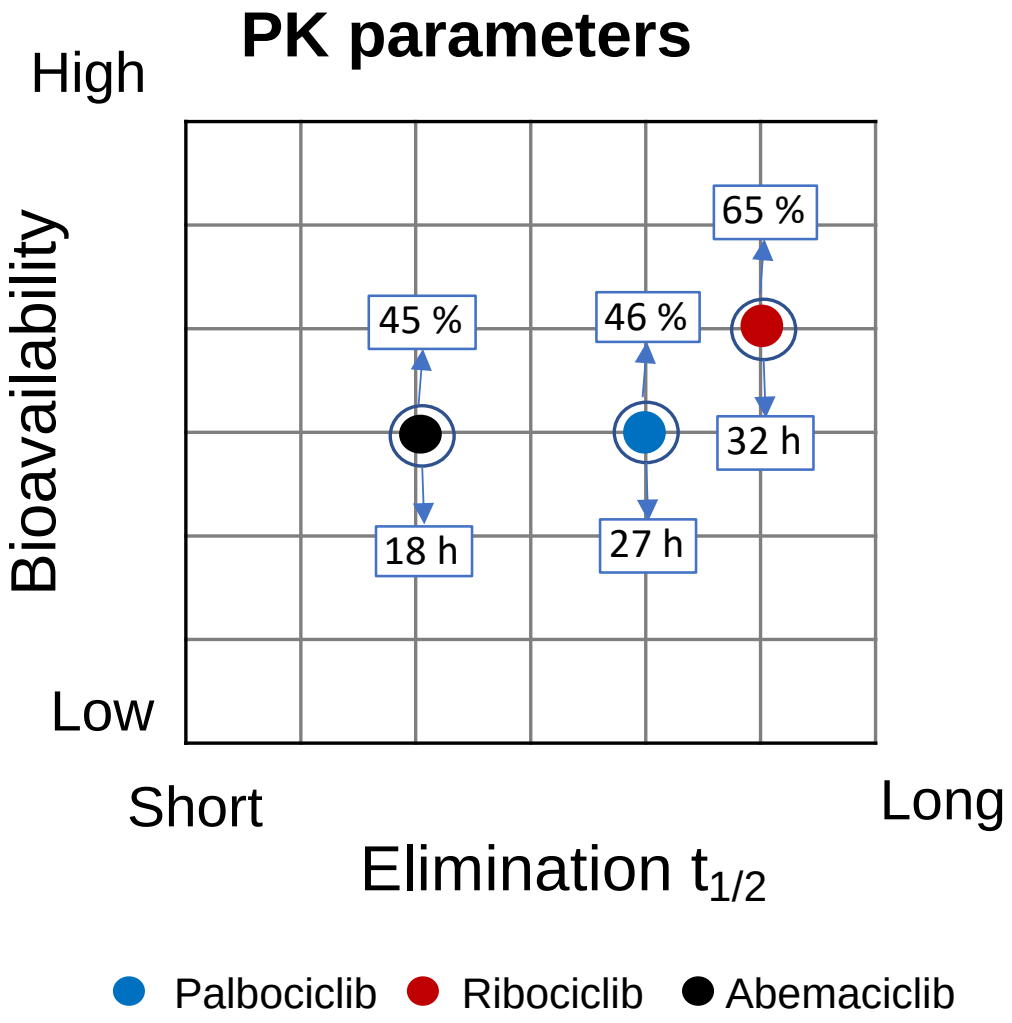
Marc Hafner et al. doi: https://doi.org/10.1101/211680

Pharmacologic differences of CDK4/6i



Danesi R et al., Unpublished

Pharmacologic differences of CDK4/6i



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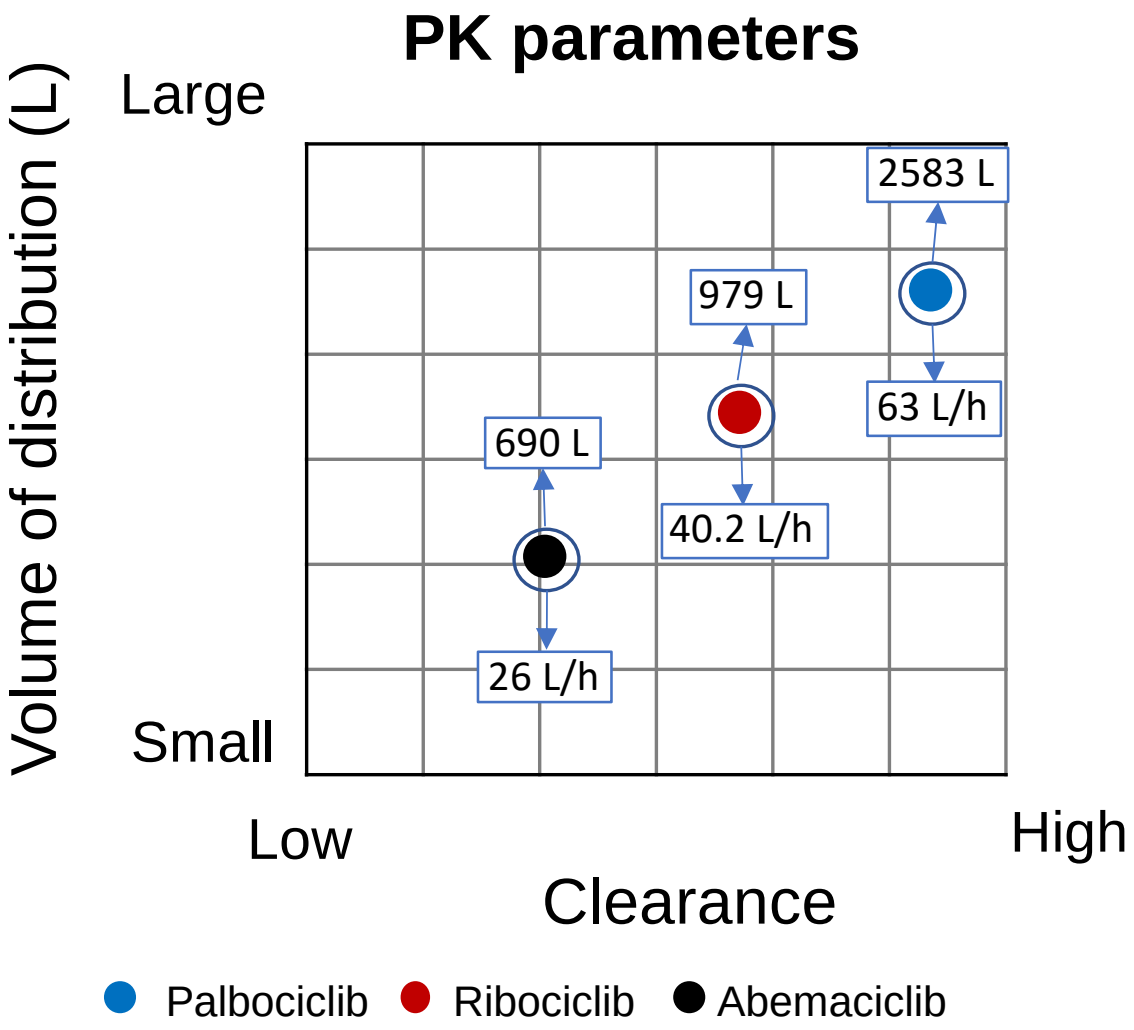
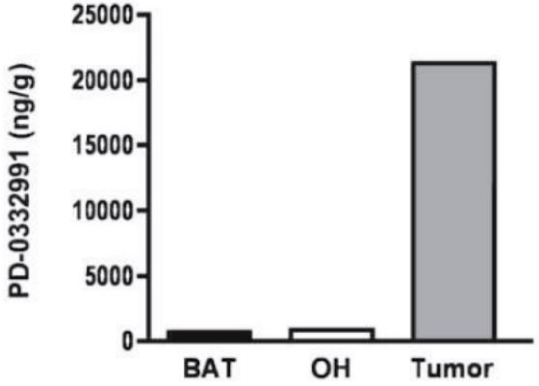
Pharmacologic differences of CDK4/6i



Danesi R et al., Unpublished

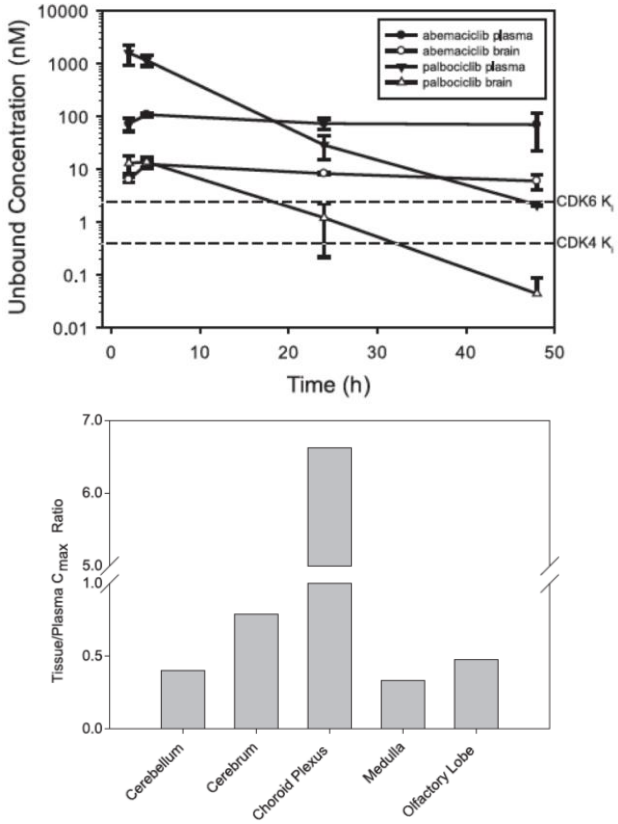
CDK4/6i and Blood Brain Barrier

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



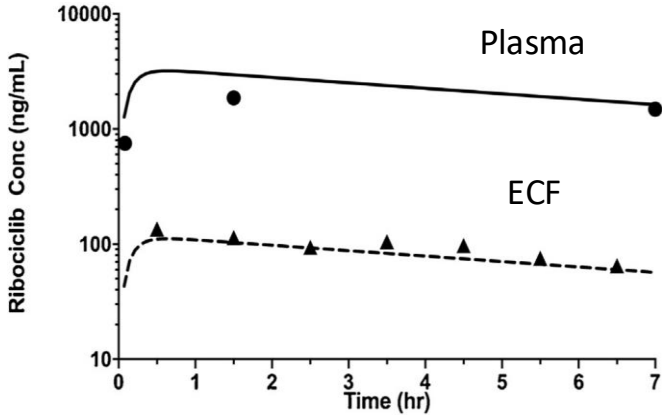
Michaud K et al. Cancer Res 2010;70:3228-3238

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



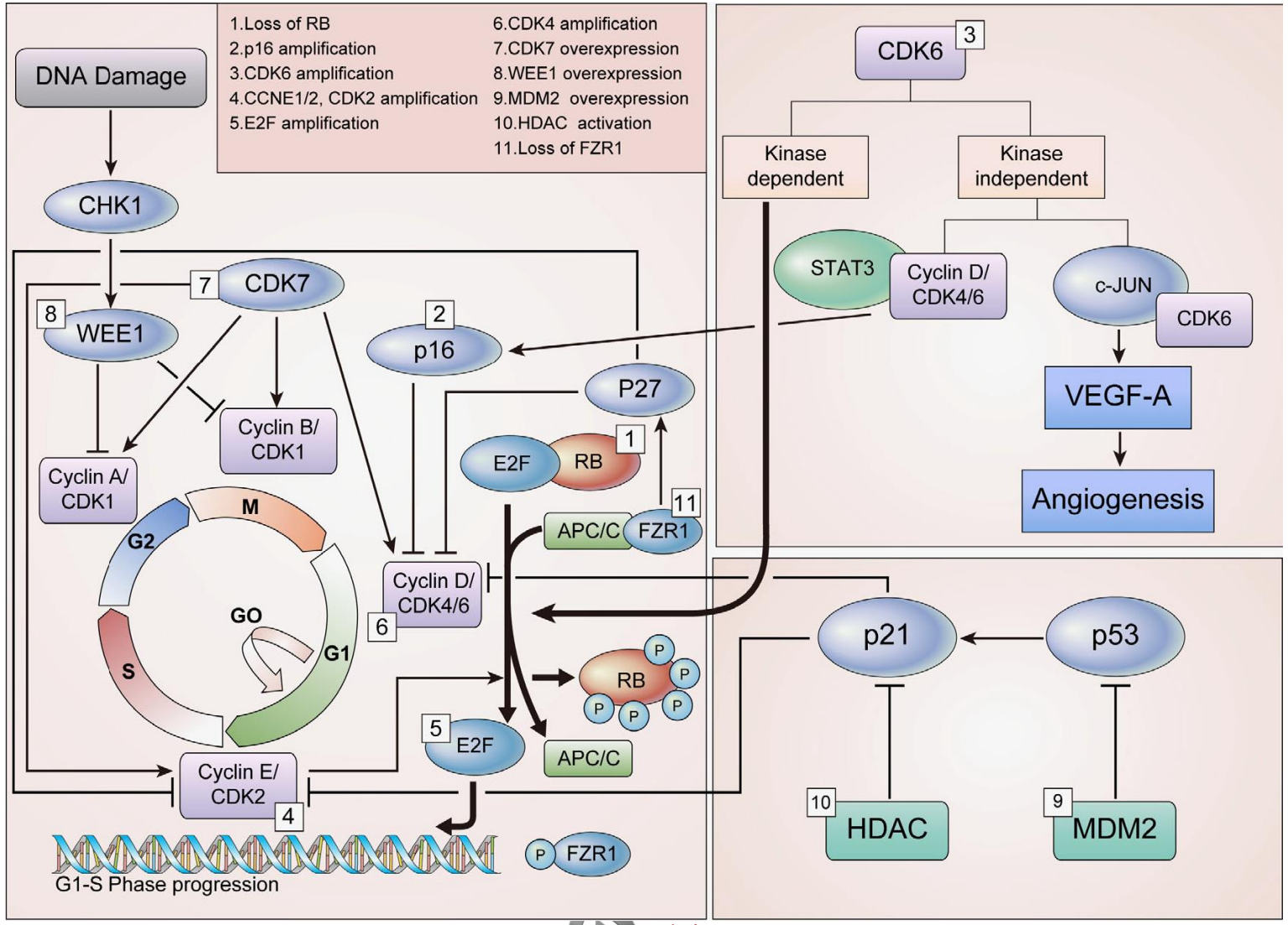
Raub TJ et al. Drug Metab Dispos 43:1360–1371, 2015

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



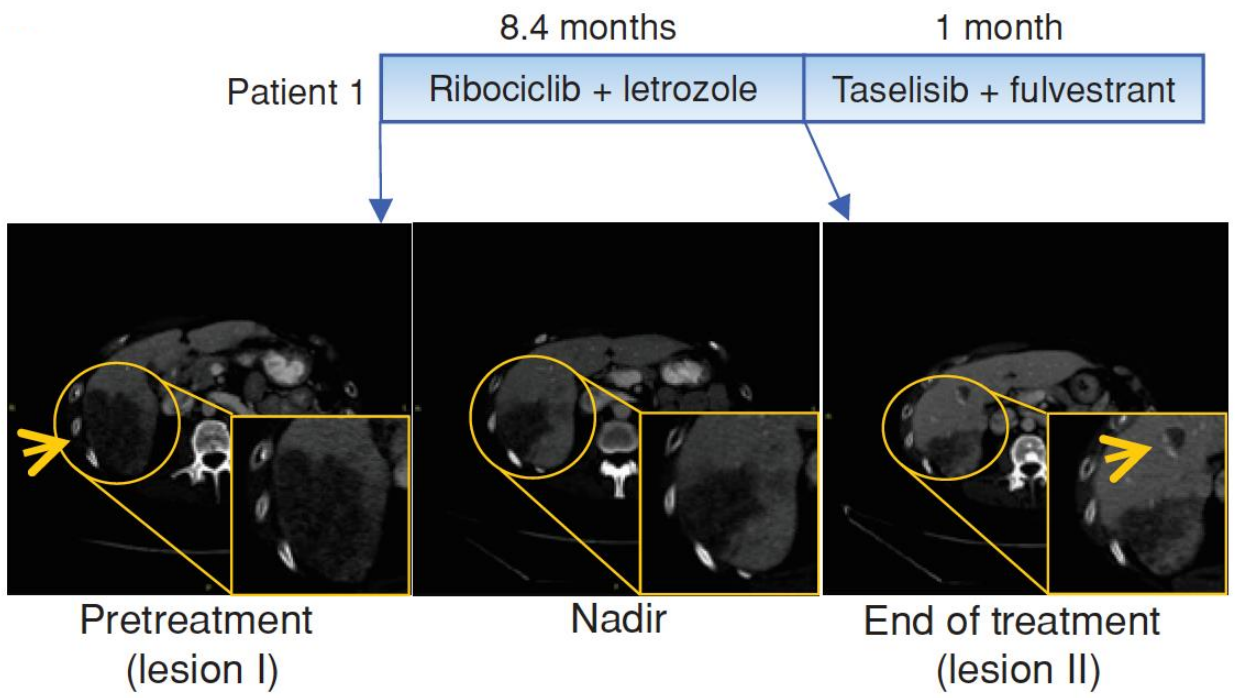
Kala A et al. J Chromatogr B 2017;1057:110–117

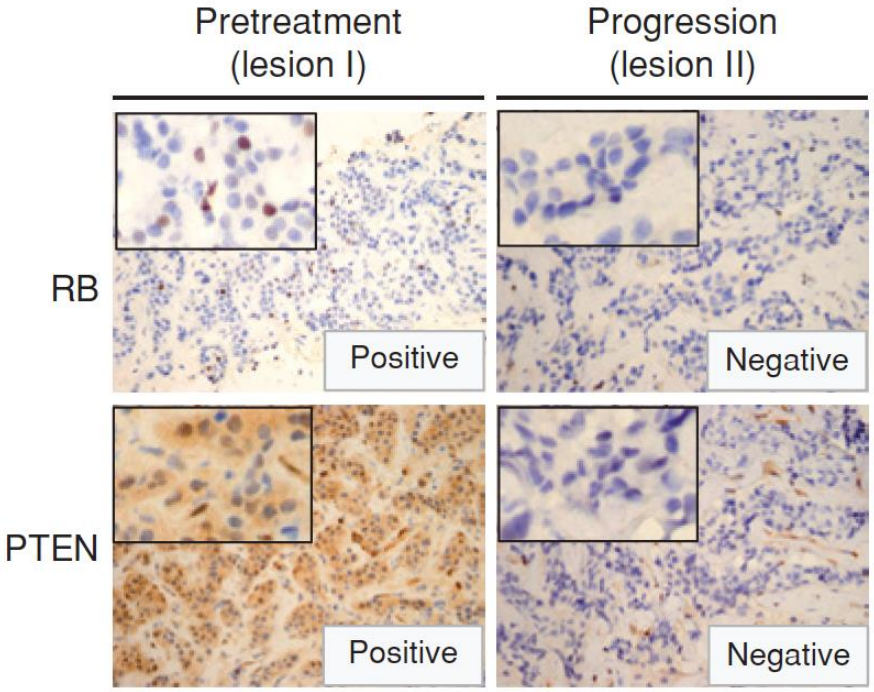
Cell cycle-specific mechanisms of CDK4/6i resistance



Pandey K et al. Int J Cancer 2019; 145:1179–1188

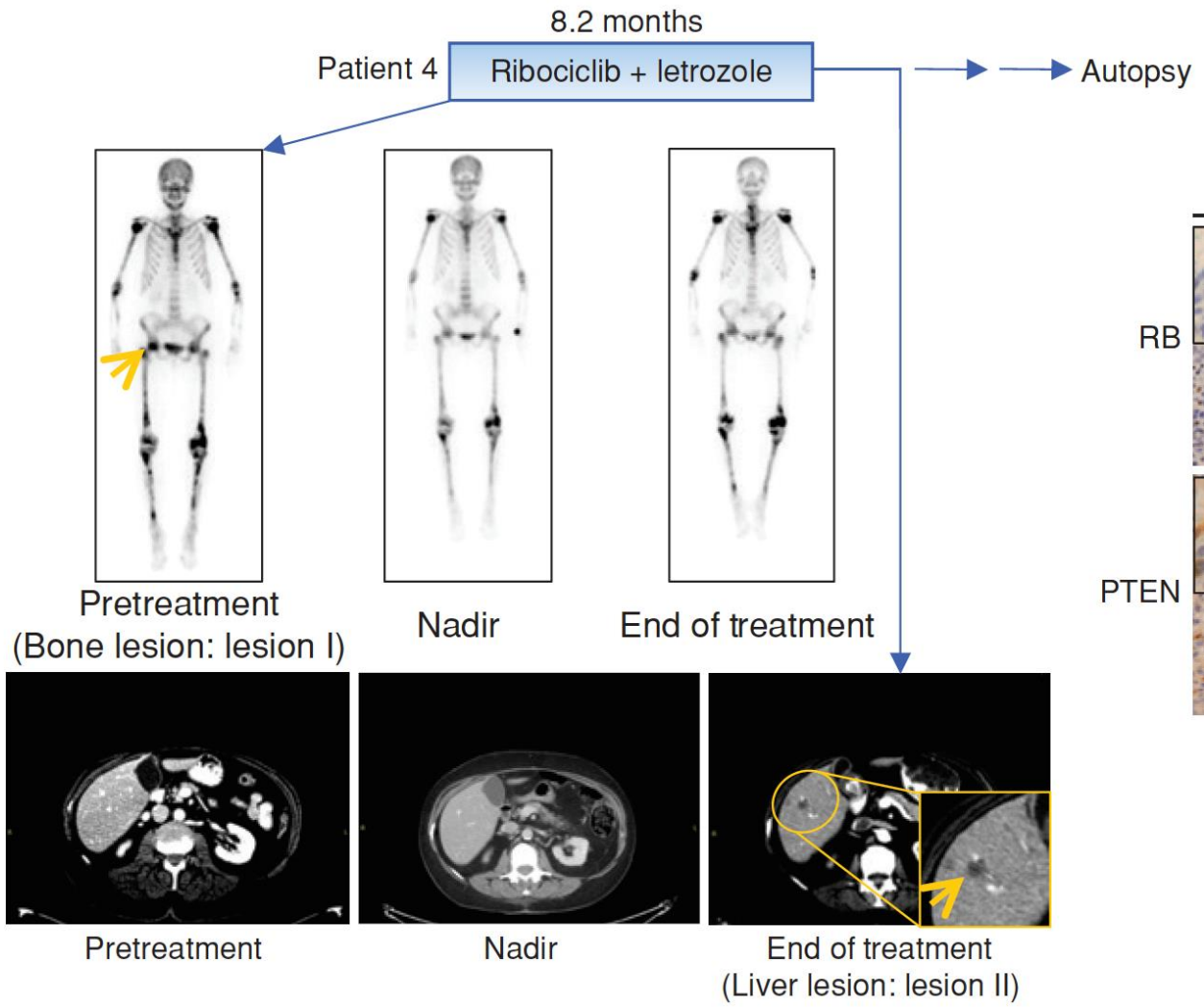
Loss of RB and PTEN in patients with acquired resistance to letrozole and CDKi

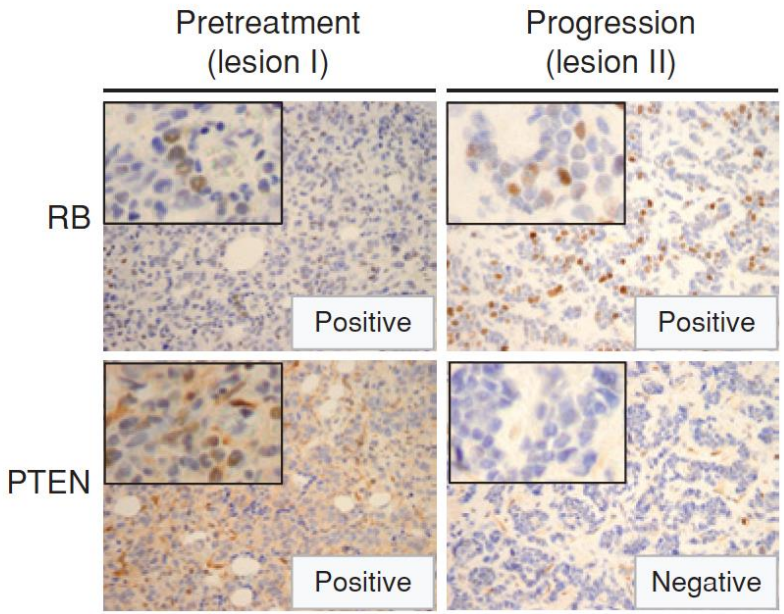




Costa C et al. Cancer Discov 2020;10:72-85

Loss of PTEN in patients with acquired resistance toCDKi





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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