

CDK4/6 inhibitors

Biomarker Research

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Disclosures

BioltaLEE Steering Committee

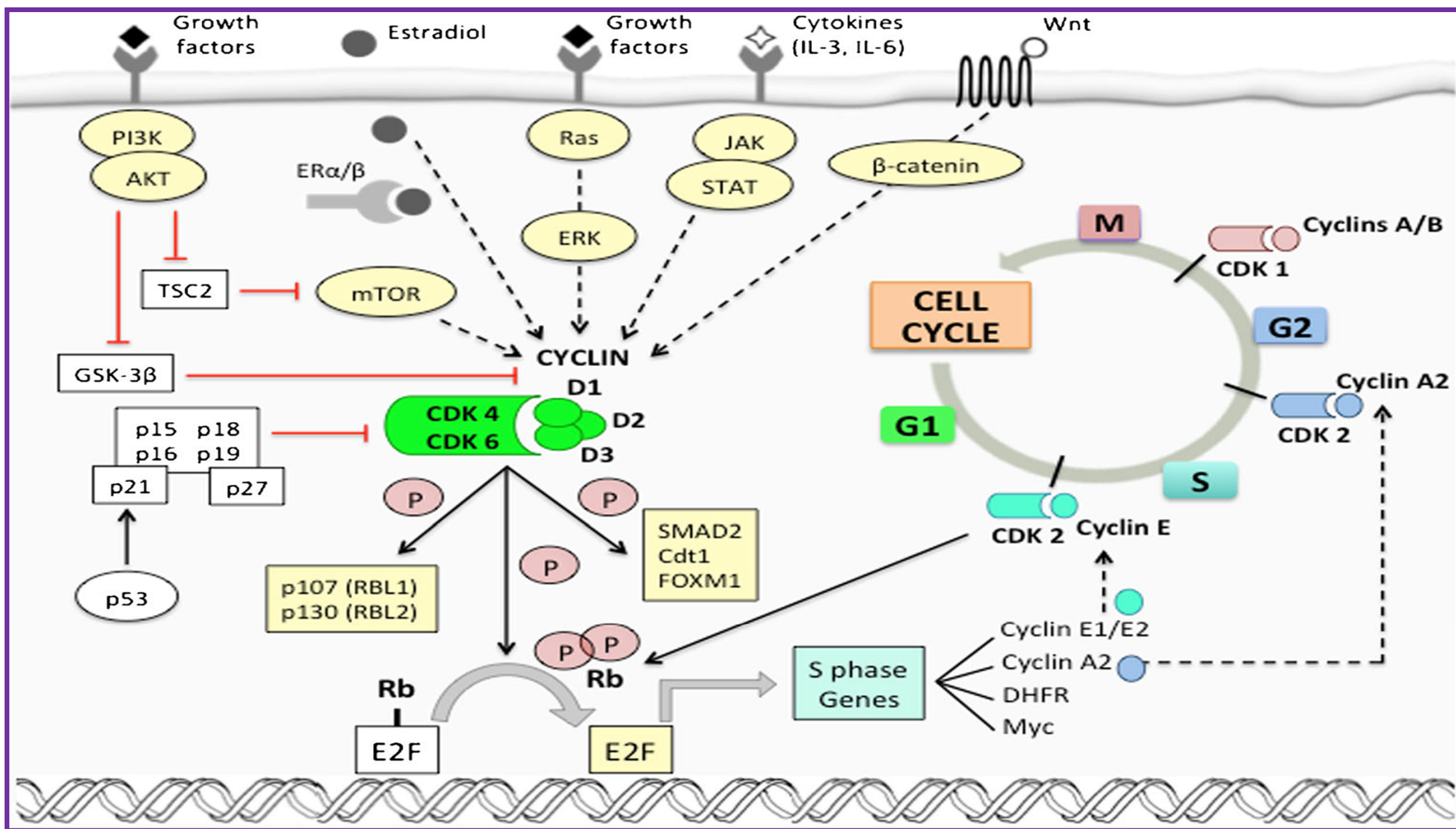


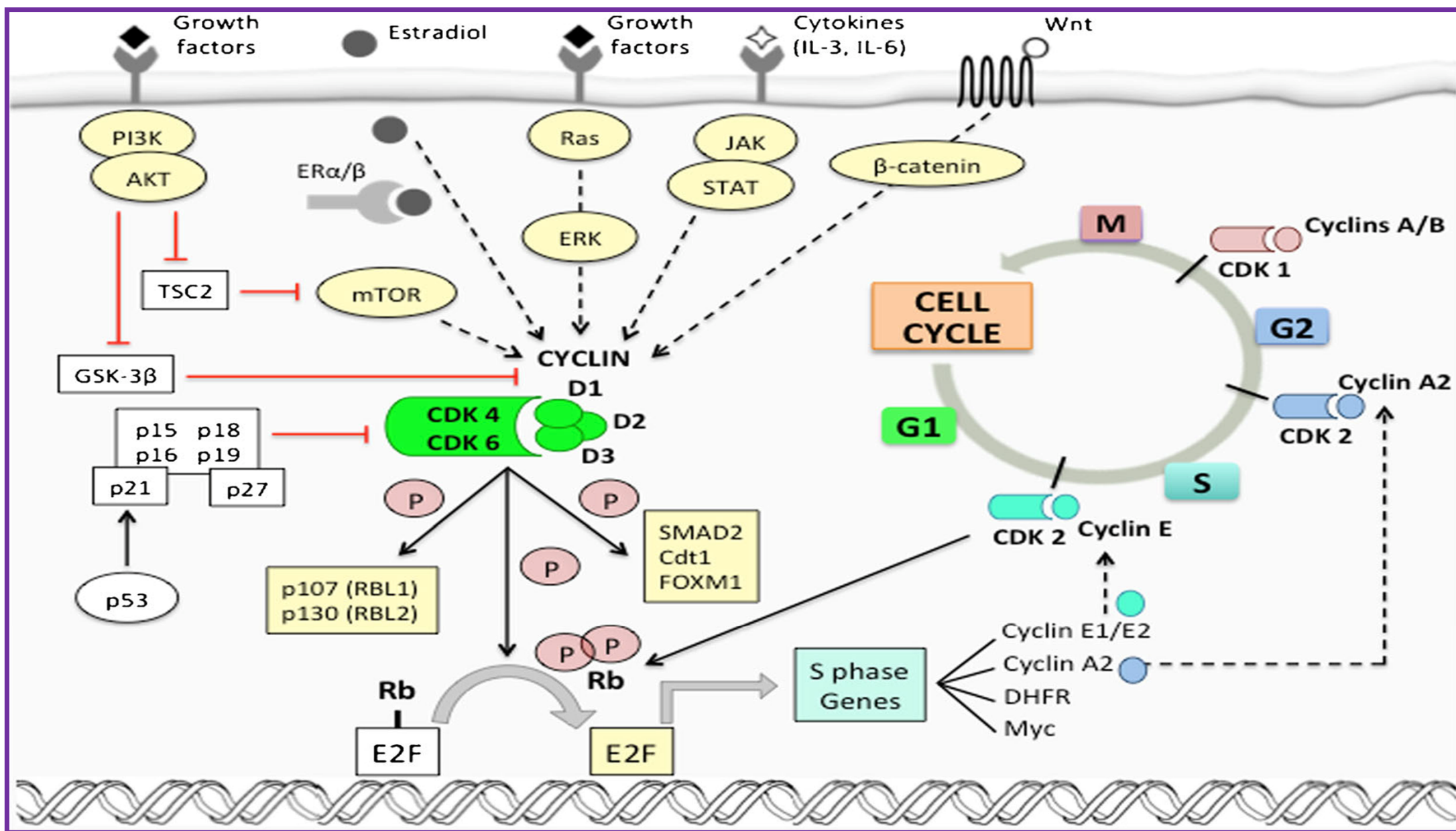
Grazia Arpino

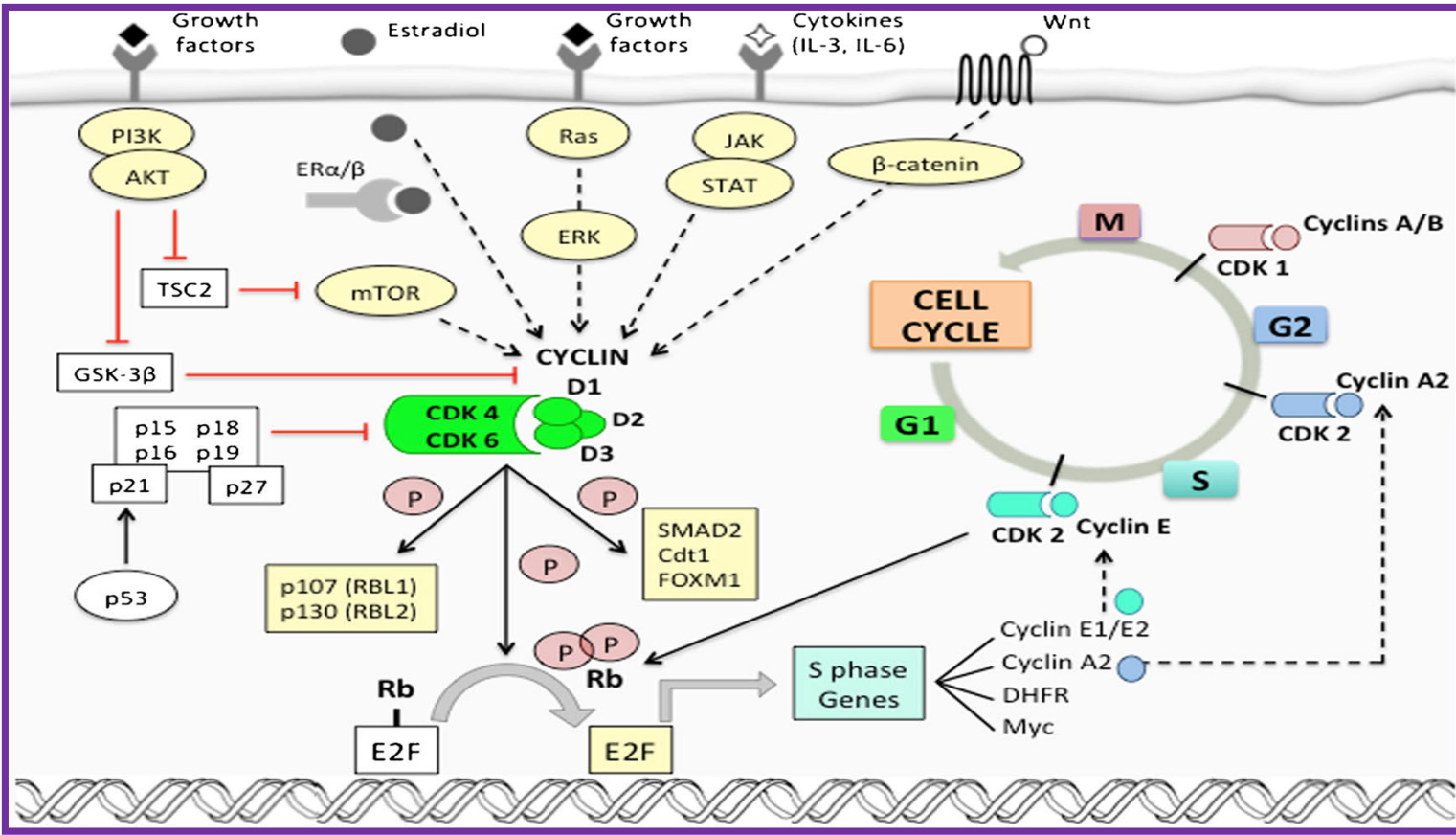
Giampaolo
Bianchini



Luca Malorni







Proliferation

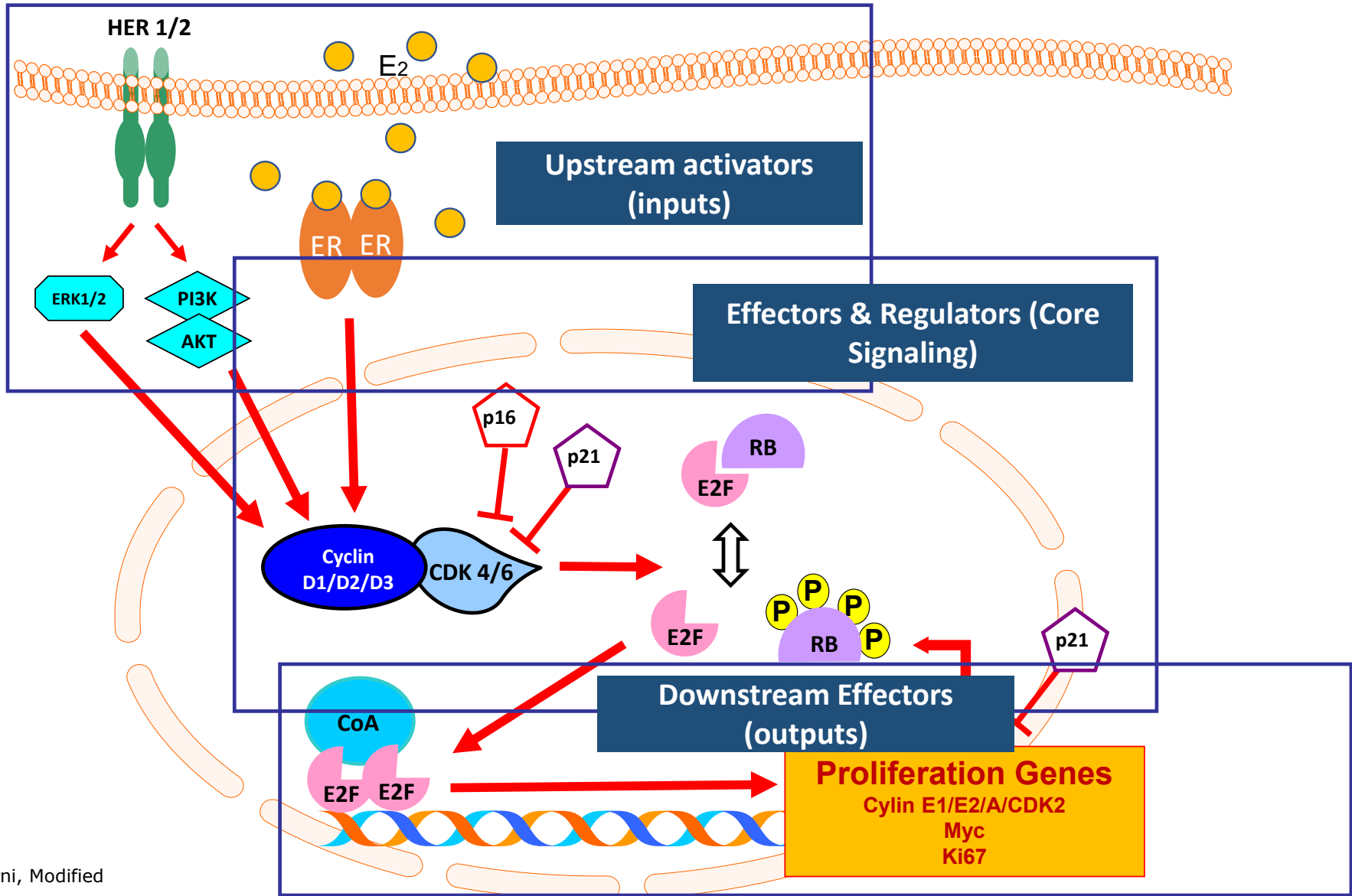


Quiescence

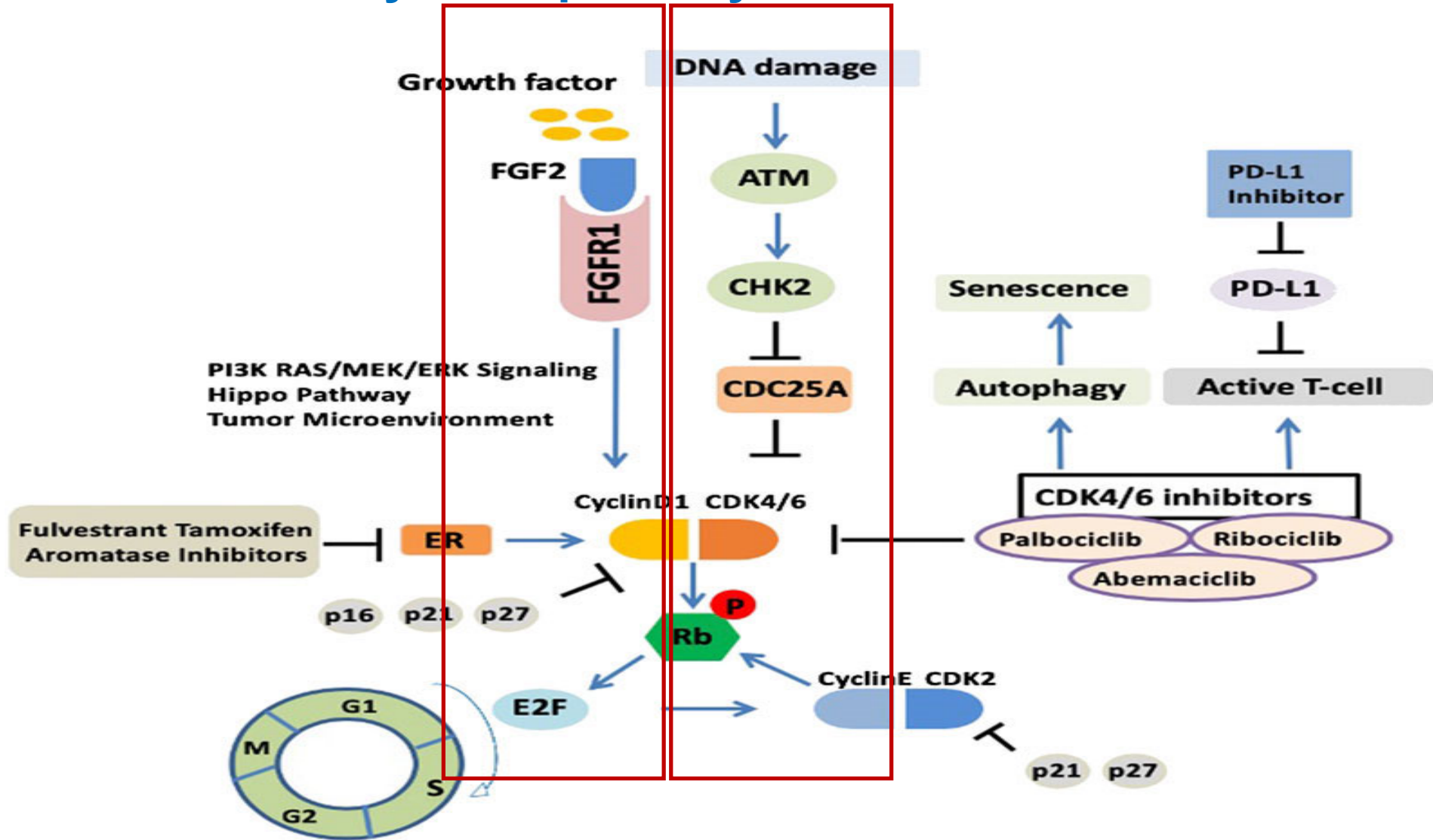


Senescence

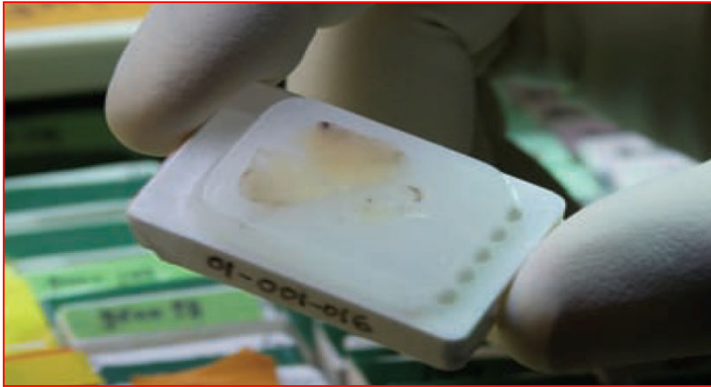
Molecular determinants of response to CDK4/6 inhibition



Potential By-Pass pathways for CDK4/6 inhibitors



Tissue Biopsy



Protein Expression

Gene Expression

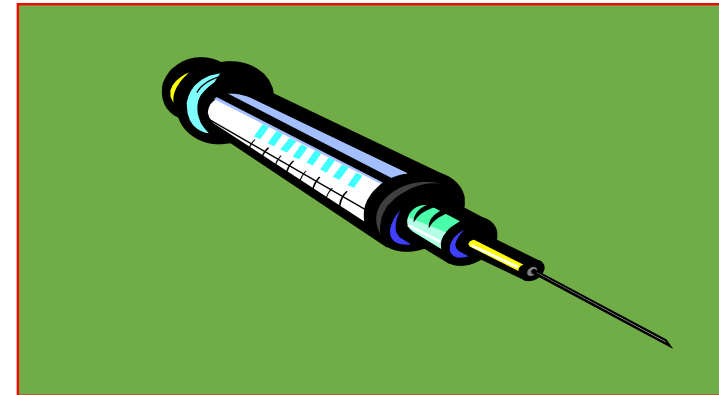
Gene Alteration

- Mutations
- Copy Number Variations

Spatial Omics

- *Architectural Distribution*

Liquid Biopsy



Ct-DNA

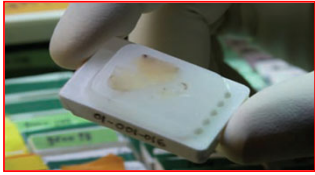
- Mutations
- Copy Number Variations

CTC

- *Mutations*
- *Copy Number Variation*
- *Gene Expression*
- *Protein Expression*

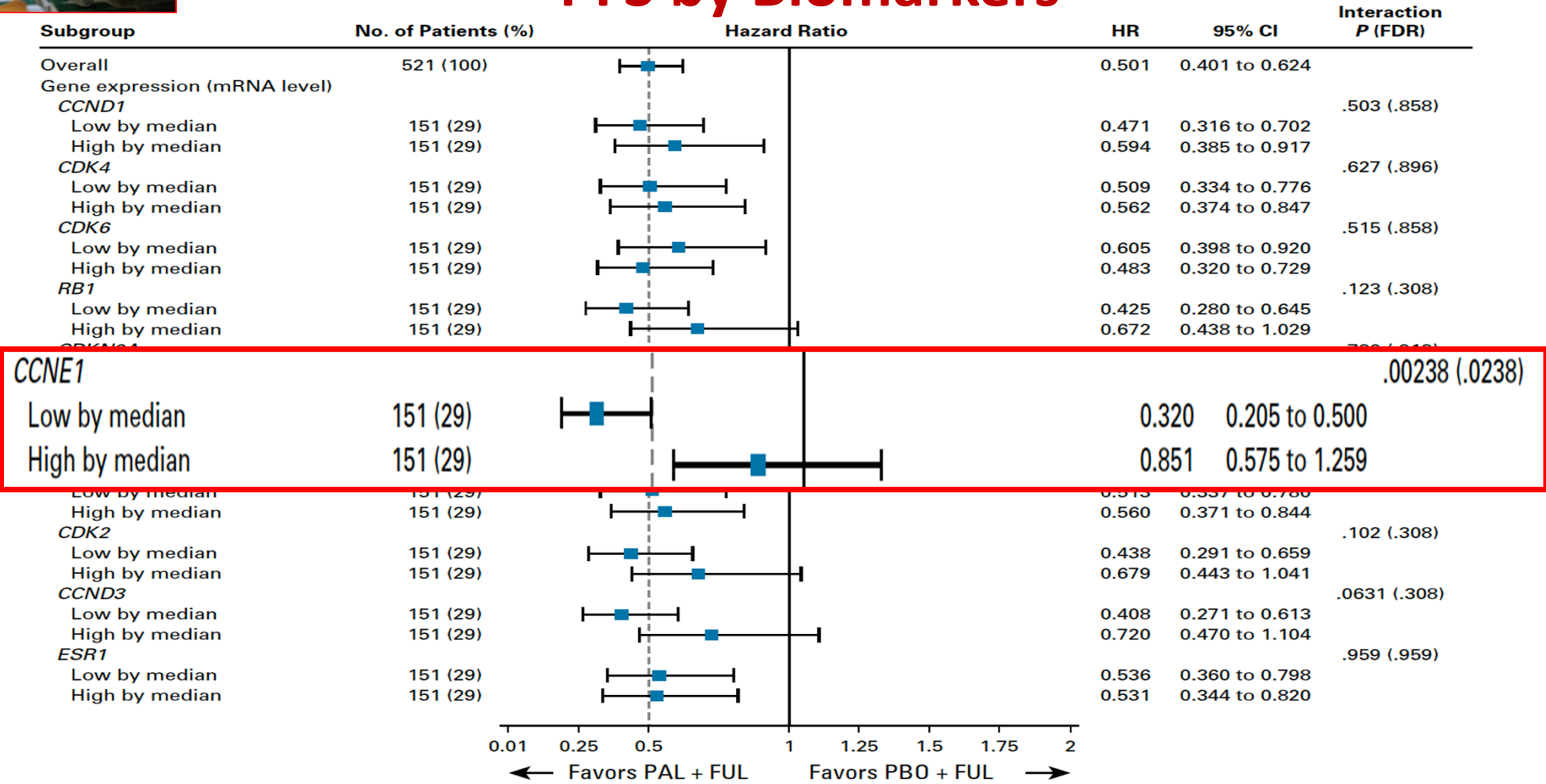
Others

- *DNA Methylation*
- *Exosomes*
- *Fragmentomics*
- *miRNA*
- *etc.*

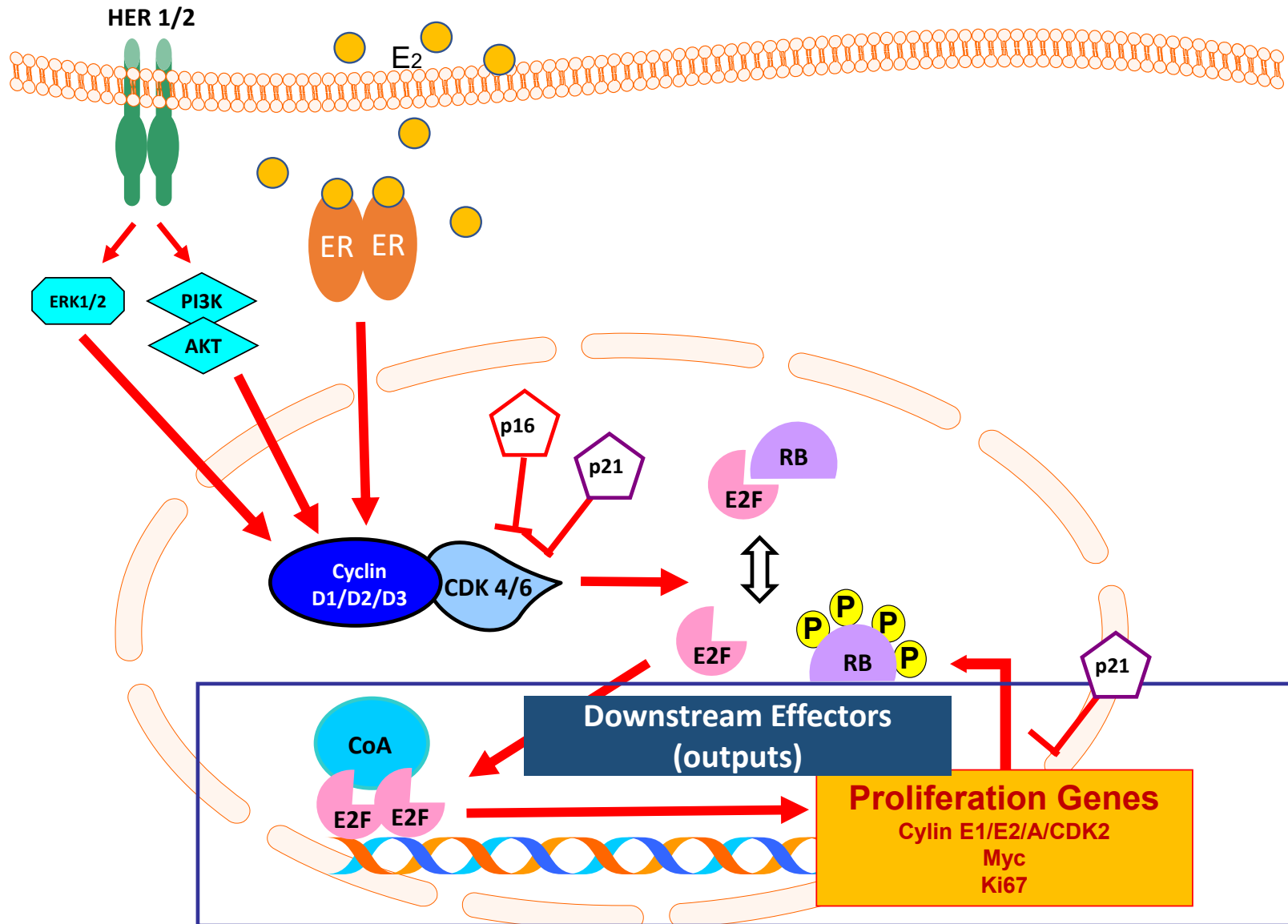


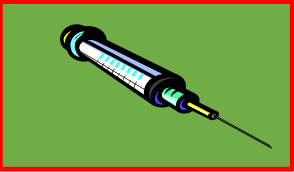
Paloma 3: PFS by Biomarkers

Gene Expression
RNAseq



Molecular determinants of response to CDK4/6 inhibition

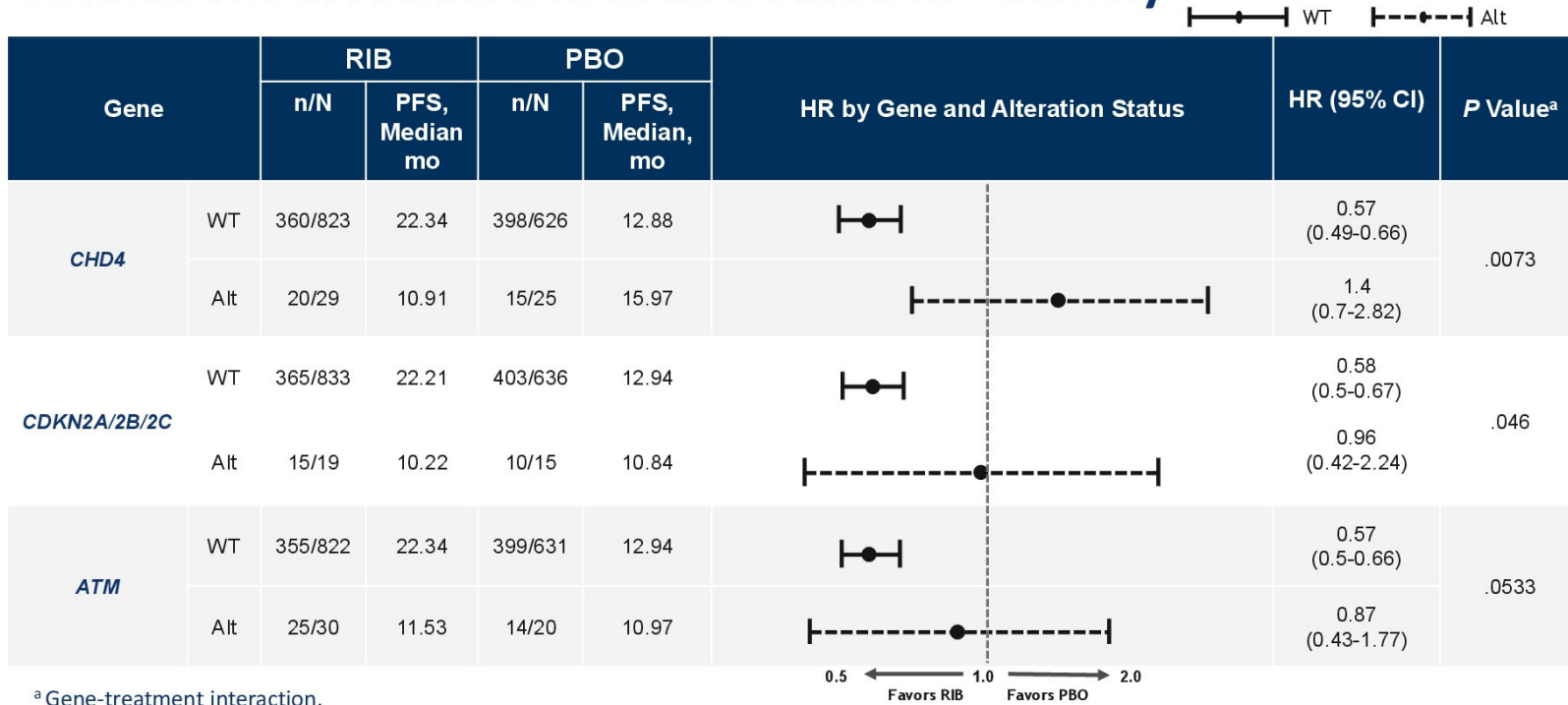




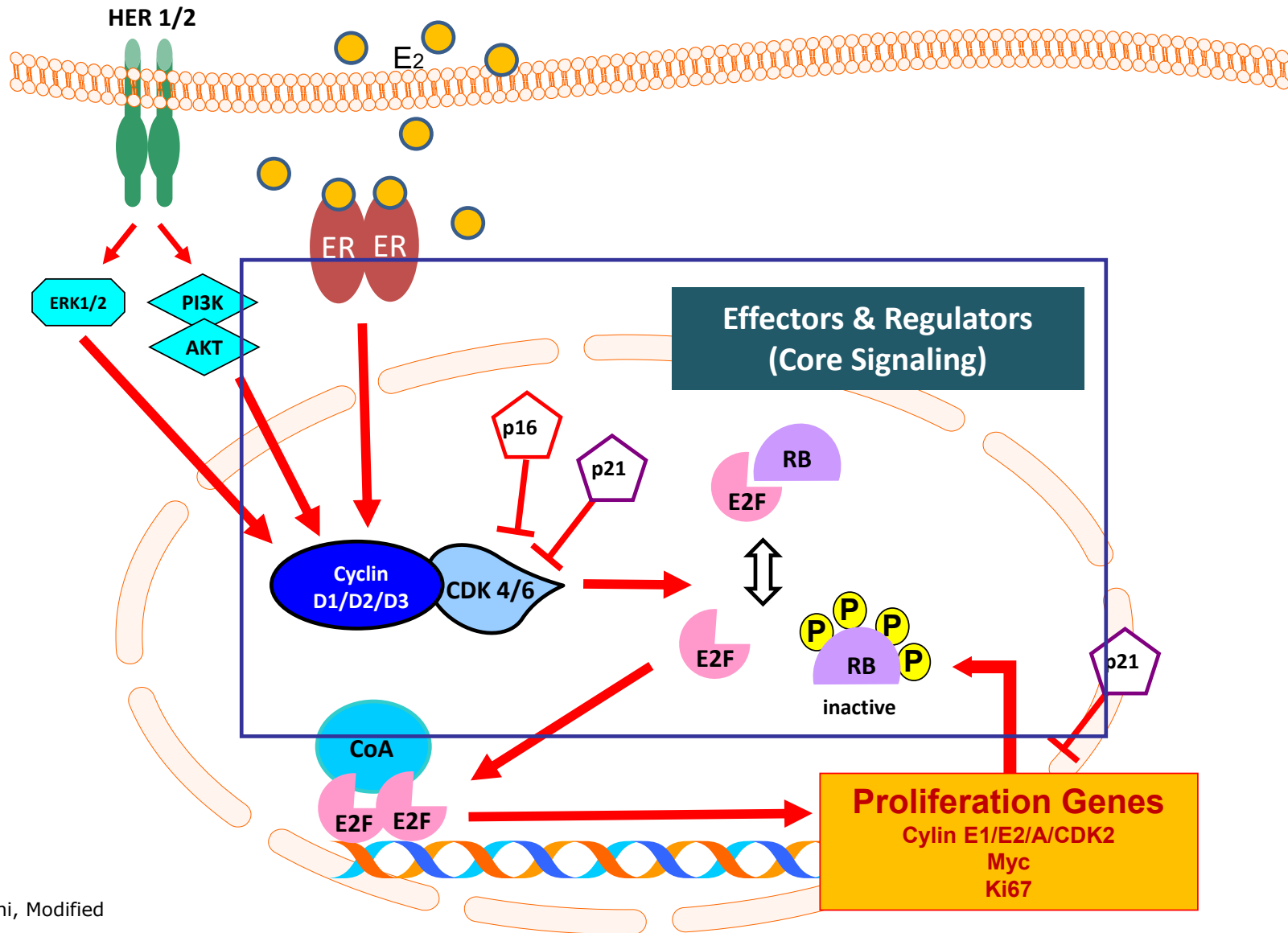
Pooled MonaLEESA Trials Analysis

Mutations
NGS

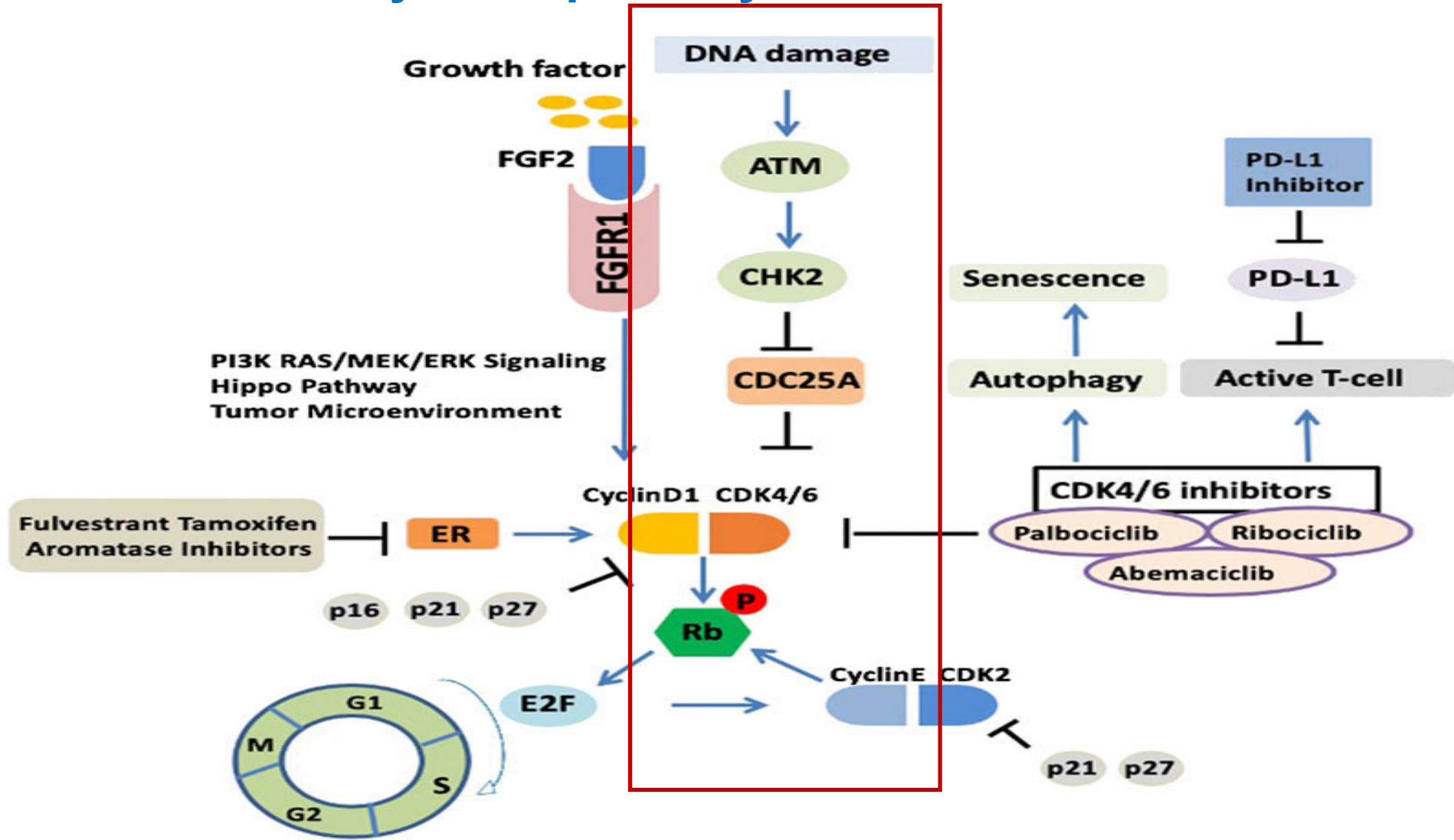
Alterations associated with decreased RIB activity



Molecular determinants of response to CDK4/6 inhibition

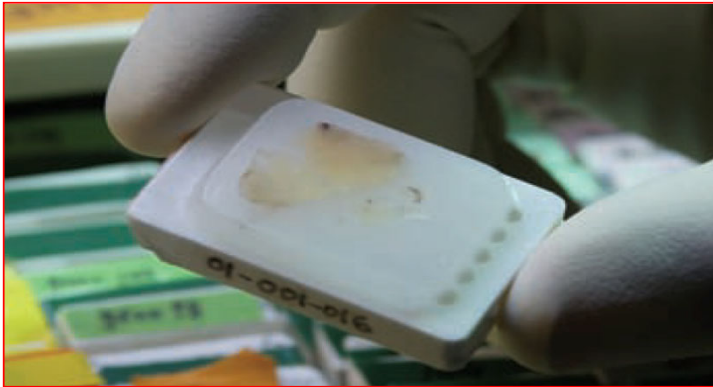


Potential By-Pass pathways for CDK4/6 inhibitors



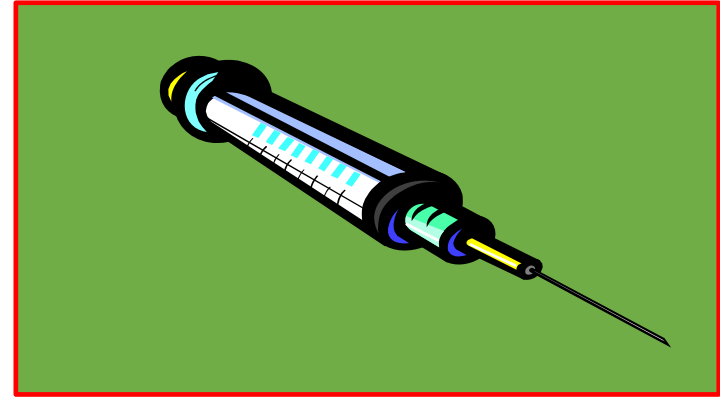
Take-Home Messages

Biopsia Tissutale



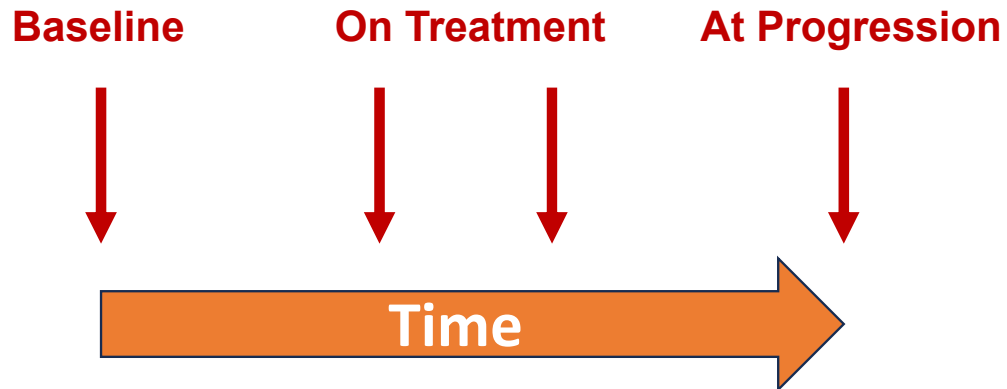
- CCNE1 high expression may be linked to resistance to CDK4/6 inhs

Biopsia Liquida

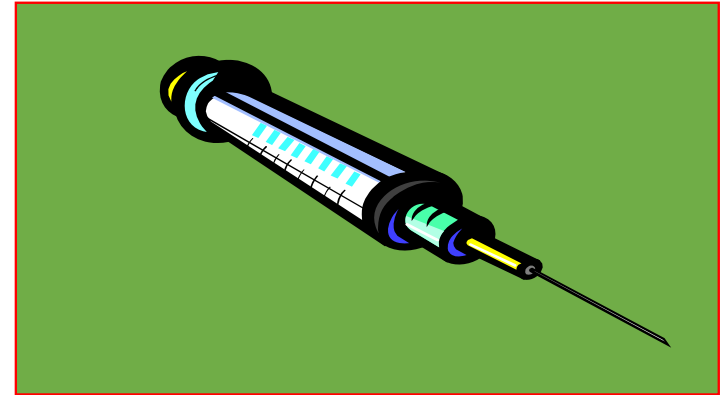


- CDKN2A/B/C, ATM and CHD4 mutations may be linked to resistance to CDK4/6 inhs

Dynamic Biomarker Evaluation



Biopsia Liquida



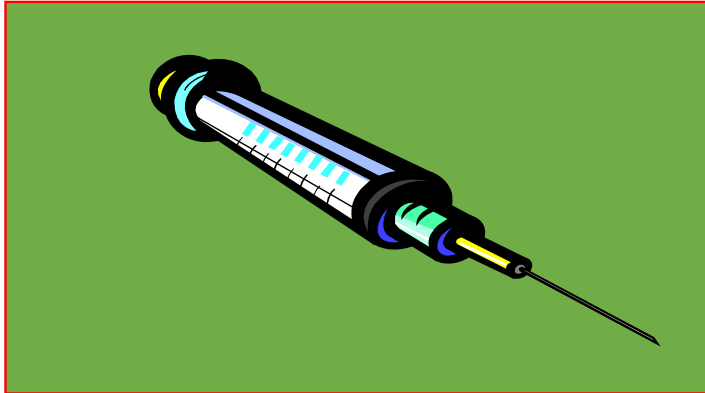
Ct-DNA

- Mutations
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CTC

- Mutations
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- Gene Expression
- Protein Expression

Biopsia Liquida



Ct-DNA

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CTC

- *Mutations*
- *Copy Number Variation*
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Others

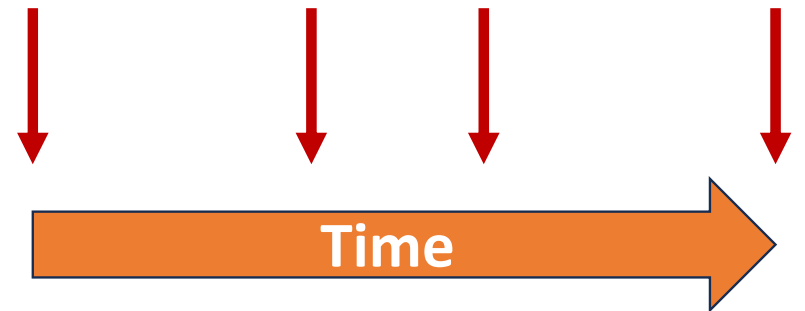
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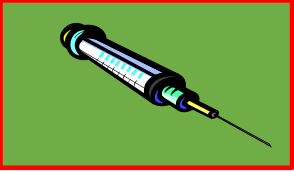
Dynamic Biomarker Evaluation

Baseline

On Treatment

At Progression



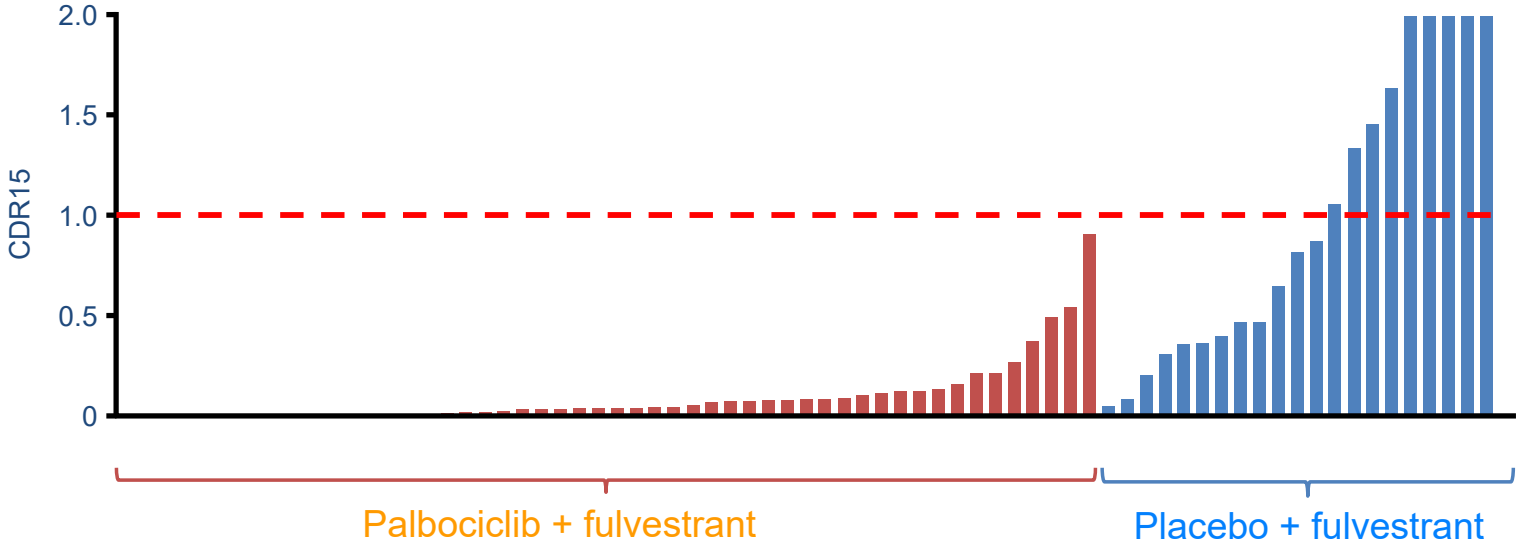


Paloma 3

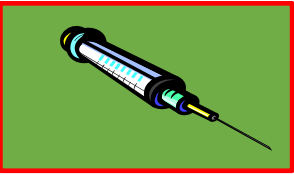
Palbociclib Suppressed PIK3CA ctDNA Levels

Mutations
NGS

Palbociclib + fulvestrant suppressed C1D15 *PIK3CA* ctDNA levels to a greater extent than placebo + fulvestrant ($P < 0.0001$)

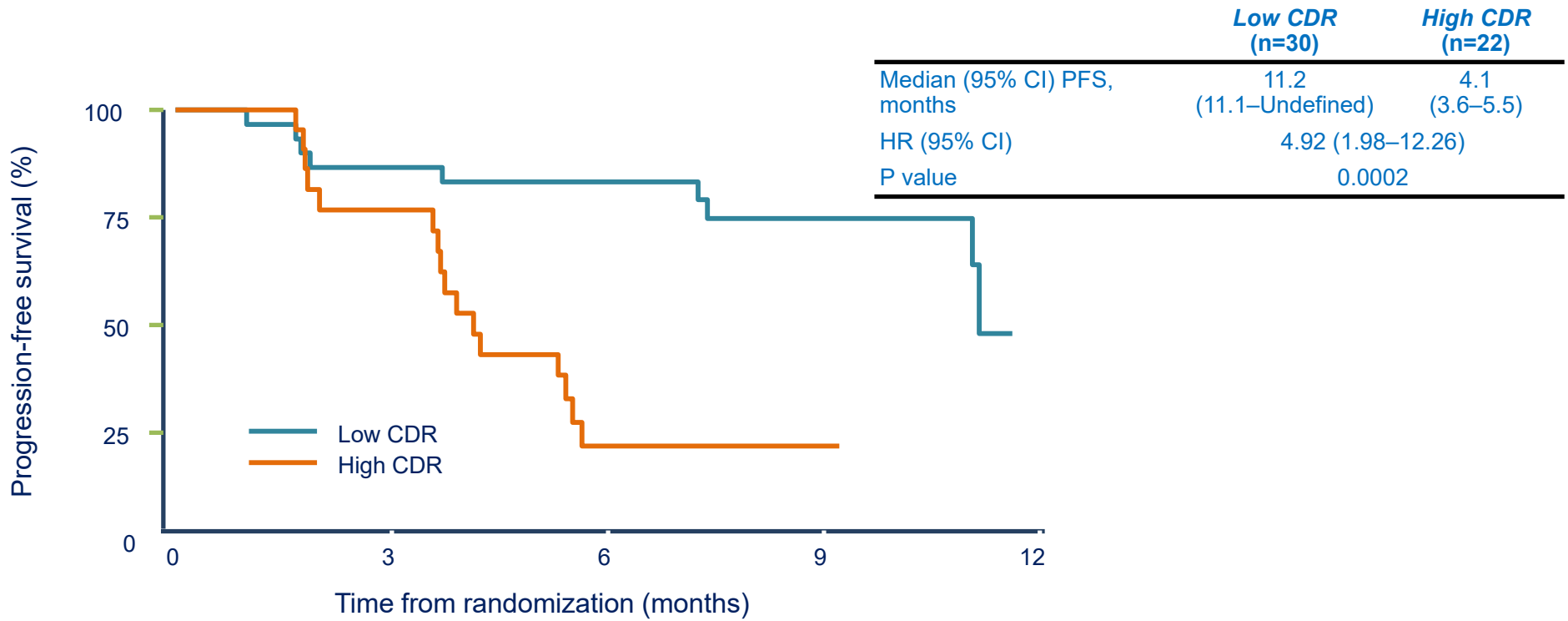


O'Leary B, et al. Nature Comm, 2018



PIK3CA ctDNA Dynamics Predicted Palbociclib Outcome

Mutations
NGS

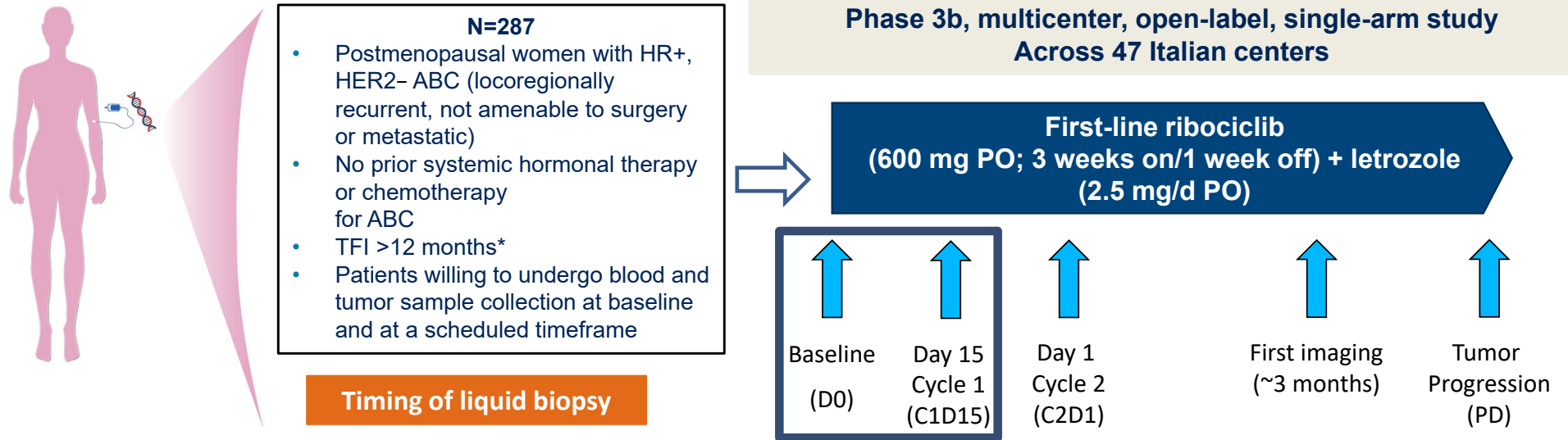


Number at risk (events)

Low CDR:	30	(4)	26	(1)	20	(2)	13	(2)	1
High CDR:	22	(5)	16	(11)	4	(0)	1	(0)	0

CDR, circulating DNA ratio; CI, confidence interval; ctDNA, circulating tumor DNA; HR, hazard ratio; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PFS, progression-free survival

BioltaLEE: Study Design



To assess prognostic/predictive value of the combined analyses of both ctDNA and TKa at baseline (D0) and day 15 (D15) of the first cycle (C1) of therapy

Study is divided into 2 phases: core phase and extension phase. Core phase: Patients who have not received any prior treatment with ribociclib+letrozole and followed up until discontinuation due to any cause. Extension Phase: Discontinued patients with *PIK3CA* mutations undergo treatment with alpelisib+fulvestrant in second-line

*If prior neo/adjuvant therapy included was letrozole or anastrozole. ABC, advanced breast cancer; C, cycle; ctDNA, circulating tumor DNA; D, day; HER2-, human epidermal growth factor receptor-2-negative; HR+, hormone receptor-positive; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PO, orally; TFI, treatment-free interval.

Biomarker analysis: ctDNA

Genes	Pathway
<i>CCND1, CCND2, CCND3, CCNE1, RB1, CDK4, CDK6, CDKN2A</i>	Cycle-related pathway
<i>EGFR, ERBB2, ERBB3, ERBB4, FGFR1, FGFR2, FGFR3, KIT, PDGFRA, MET, RET</i>	RTK pathway
<i>KRAS, NRAS, HRAS, MAP2K1, MAP2K4, MAP3K1</i>	MAPK pathway
<i>AKT1, PIK3CA, PIK3R1, PTEN</i>	PI3K pathway
<i>ATM, CDKN2A, TP53</i>	P53 pathway
<i>EGFR, ERBB2, ERBB3, ERBB4</i>	HER family pathway
<i>FGFR1, FGFR2, FGFR3</i>	FGFR pathway
<i>CCND1, RB1, CDK4, CDK6, CDKN2A</i>	CDK4/6 pathway
<i>ATM, TP53, MLH1, MSH2</i>	DNA repair pathway
<i>ESR1, GATA3, KMT2C, MYC, RUNX1</i>	ERnf pathway

CDK, cyclin-dependent kinase; DNA, deoxyribonucleic acid; ERnf, estrogen receptor nuclear function; HER, human epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; MAPK, mitogen-activated protein kinase; PIK3CA, phosphoinositide-3-kinase, catalytic, alpha polypeptide; RTK, receptor tyrosine kinases

BioltaLEE: Participating Centers

