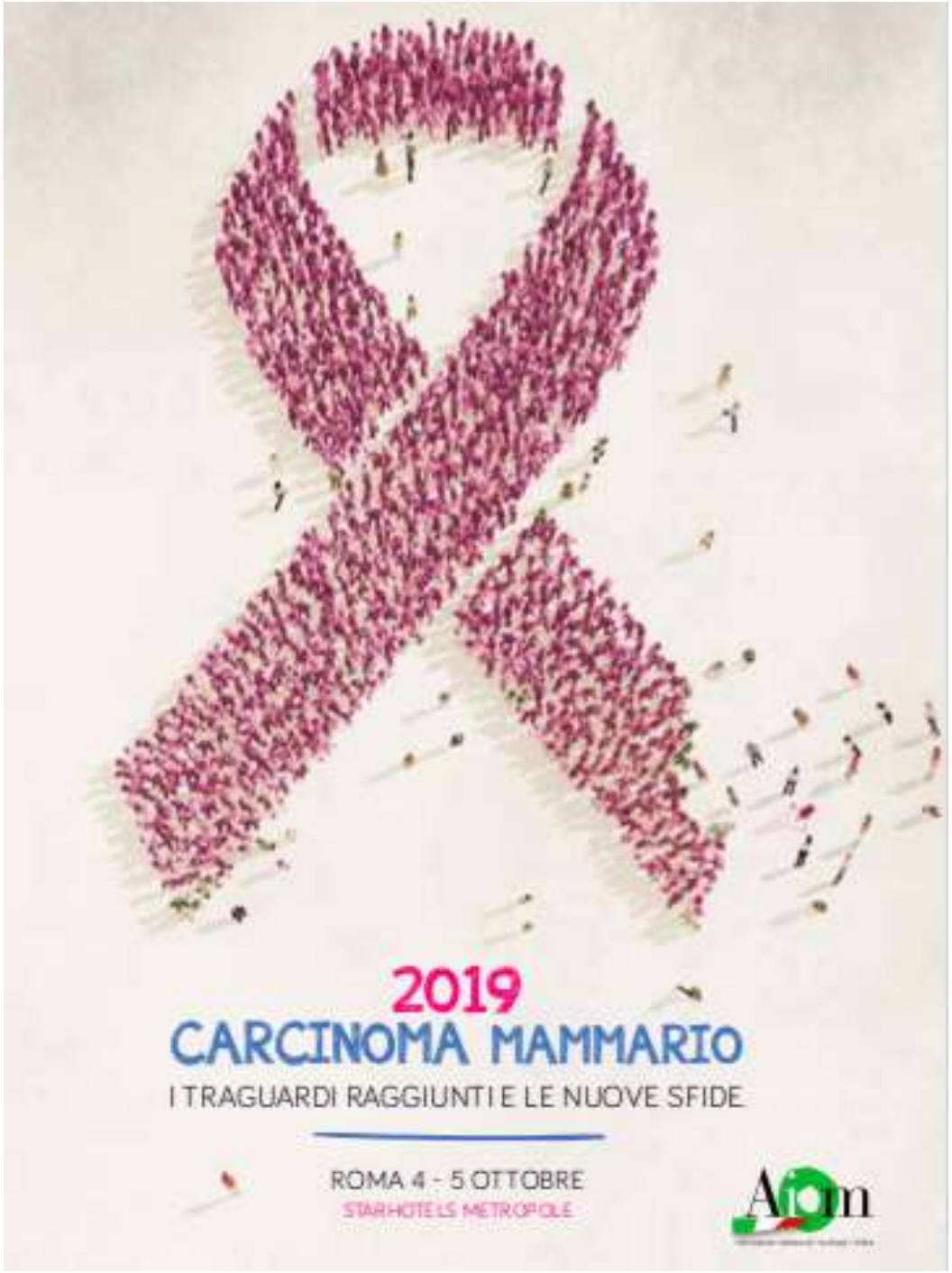

Markers genomici di resistenza ai CDK4/6 inhibitors: i dati degli studi clinici e della real world.

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Introduction

1. 60-70% of BC is HR+. Hormone therapy represents the mainstay therapy for HR+ BC.

2. **CDK4/6 inhibitors** are highly effective in HR+/HER2- mBC with long-term survival improvements in the upfront setting as well as in pts previously treated with ET for advanced disease and they are now **largely used in clinical practice**.

3. ***De novo* or acquired resistance** inevitably occur with different mechanisms, most of which are still unknown.

4. Identification of **biomarkers** is important to recognize **patients benefitting the most** from CDK4/6i as well as to clarify **mechanisms of resistance** that could lead to a rational selection of patients to candidate for combination therapies.

Deregulation of CDK regulatory genes in cancer

The cyclin-CDK-RB axis is critical to cell cycle entry.

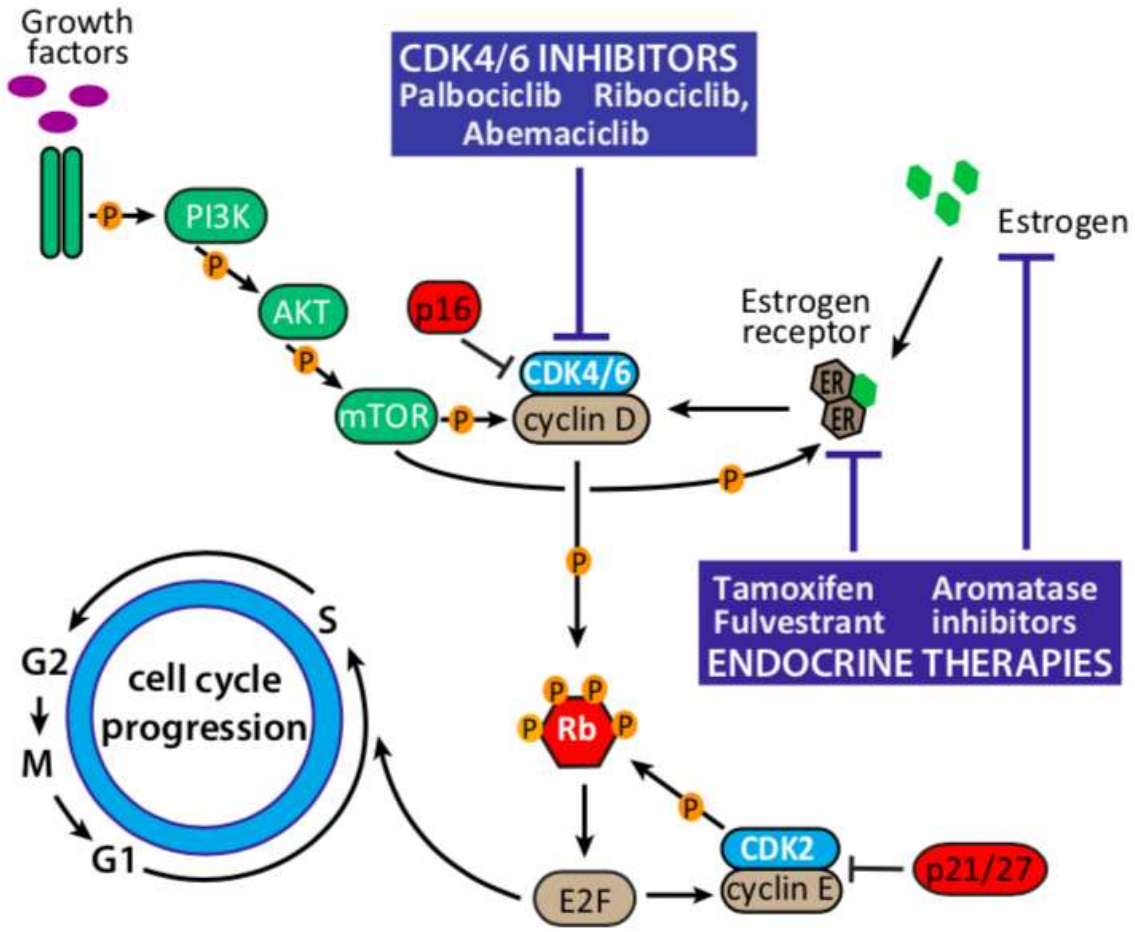
The vast majority of cancers subvert this axis to promote proliferation.

Most common mechanisms include:

- Upregulation of cyclins (D1 in breast cancer, E1 and E2 in endometrial and ovarian cancers)
- Oncogenic activation of CDK4/6 activity
- Abrogation of suppressors (Rb loss in SCLC, p16INK4A loss in glioblastoma)

CDK inhibitors are pharmacological agents used to target dysregulated CDK activity in malignant cells.

Regulation of cell cycle in ER+ breast cancer



ER positive breast cancer growth depends on cyclin D1.

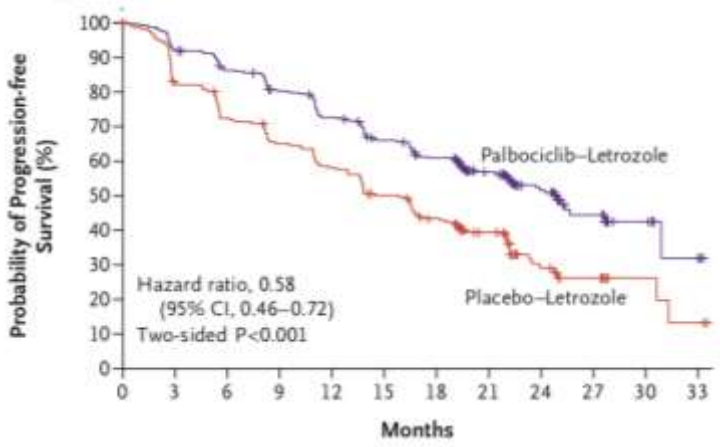
Cyclin D1 expression is regulated by multiple factors:

1. CCND1 amplification (30% ER+ BC)
2. ER signaling
3. Mitogenic signaling (PI3K, MAPK..)

Portman N, et al. *Endocrine-Related Cancer* 2019

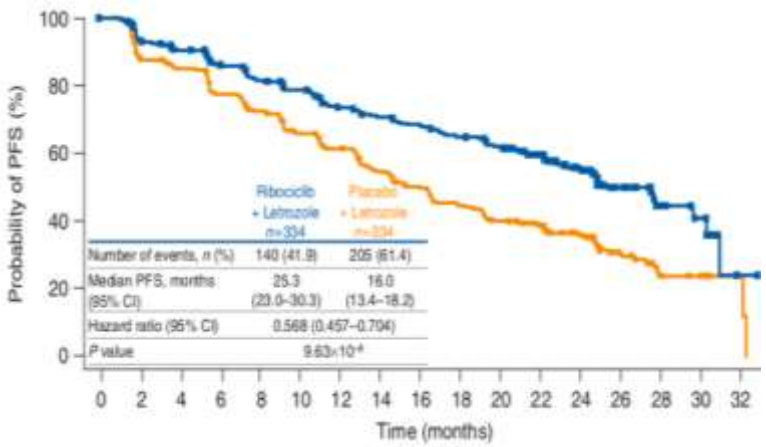
CDK4/6 inhibitors clinical outcomes – 1° line

PALOMA-2



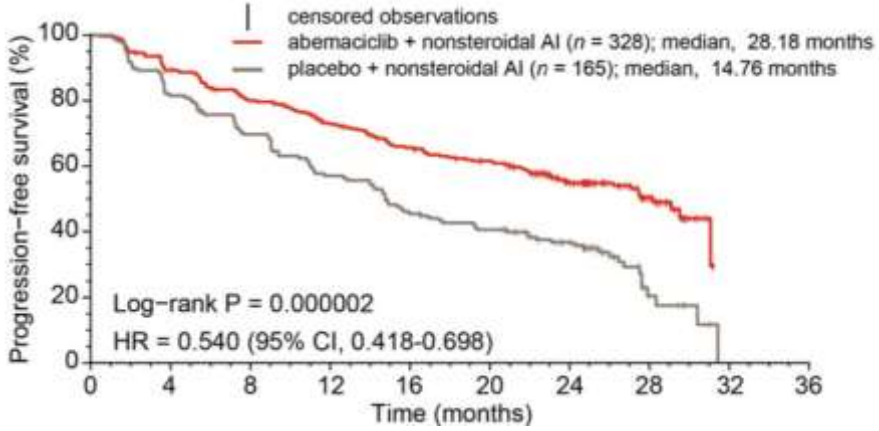
Finn et al. *NEJM* 2016

MONALEESA-2



Hortobagyi et al. *NEJM* 2016

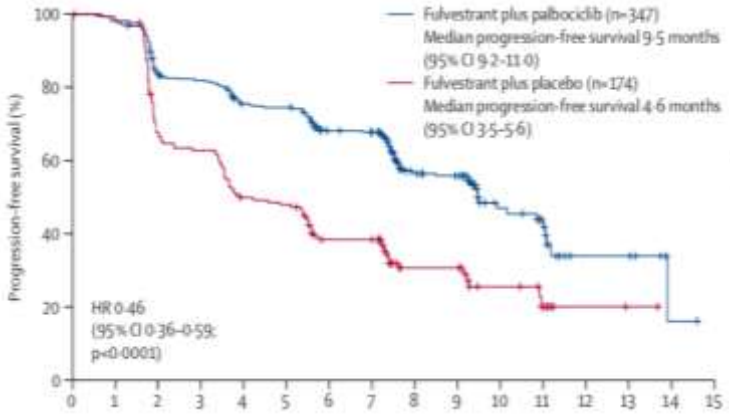
MONARCH-3



Johnston et al. *Breast Cancer* 2019

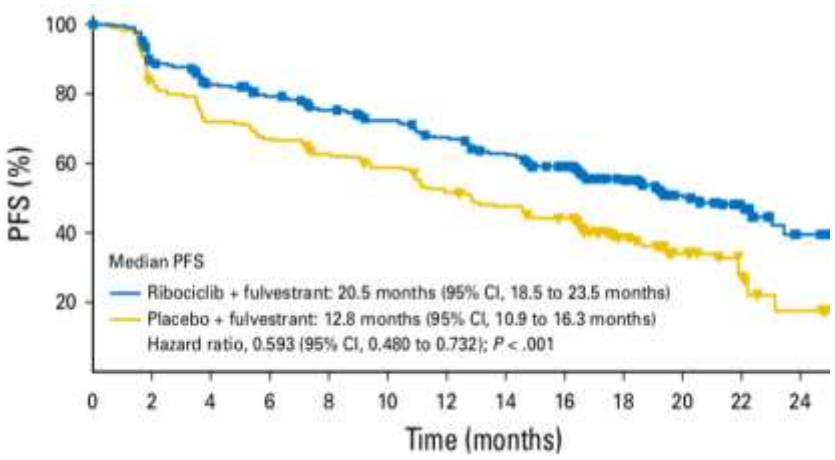
CDK4/6 inhibitors clinical outcomes – 2° line

PALOMA-3



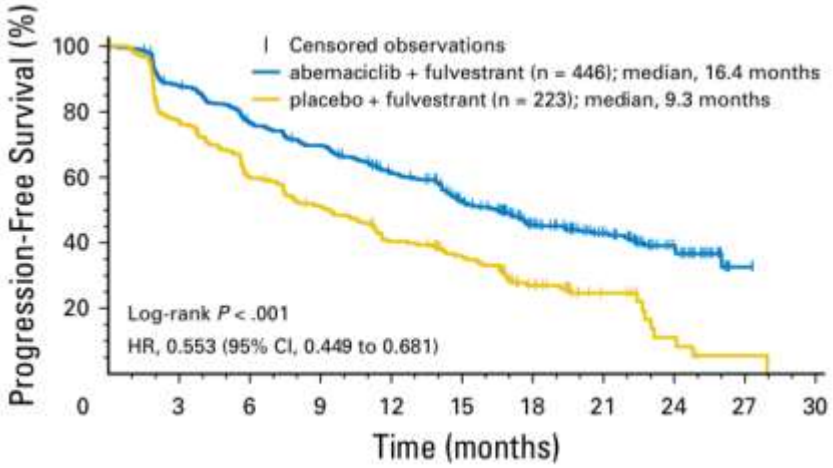
Cristofanilli et al. *Lancet Oncol* 2016

MONALEESA-3



Slamon et al. *JCO* 2018

MONARCH-2



Sledge et al. *JCO* 2017

CDK4/6 inhibitors resistance mechanisms

Despite improved disease control with CDK4/6 inhibitors in HR-positive breast cancer, not all patients respond to these drugs and most patients develop resistance.

According to the time of appearance of drug resistance, underlying mechanisms can be divided into:

→ ***de novo* resistance**

→ **acquired resistance**

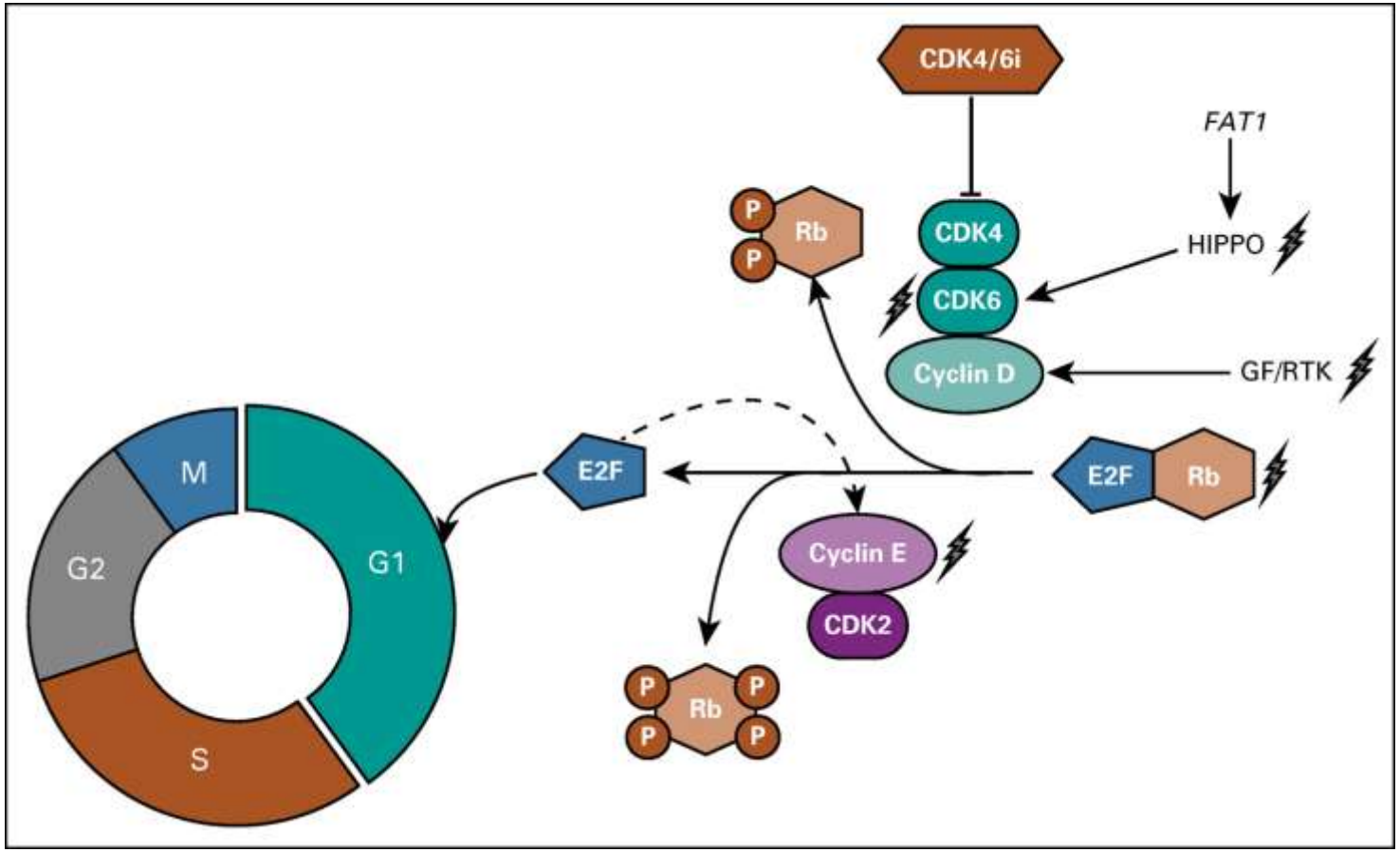
Another way of classification refers to the dysregulation of intracellular signaling pathways: mechanisms of resistance can be cell cycle specific or cell cycle non-specific.

CDK4/6i resistance mechanisms from preclinical studies

1. **RB1 loss or mutation**
2. **CDK6 amplification**
3. **CCNE1/2, CDK2 amplification**
4. **E2F amplification**
5. p16 amplification
6. Cyclin D1 amplification
7. Activation of the FGFR pathway
8. Activation of the PI3K/AKT/mTOR pathway
9. Loss of ER or PgR expression
10. Immune mechanisms

Pandey et al. *IJC* 2018

Potential mechanisms of resistance with hyperactivation of CDK4/6 activity



Chandarlapaty and Razavi, *JCO* 2019

RB1 mutations and resistance to CDK4/6i

Annals of Oncology 29: 640–645, 2018
doi:10.1093/annonc/mdx784
Published online 11 December 2017

ORIGINAL ARTICLE

Polyclonal *RB1* mutations and acquired resistance to CDK 4/6 inhibitors in patients with metastatic breast cancer

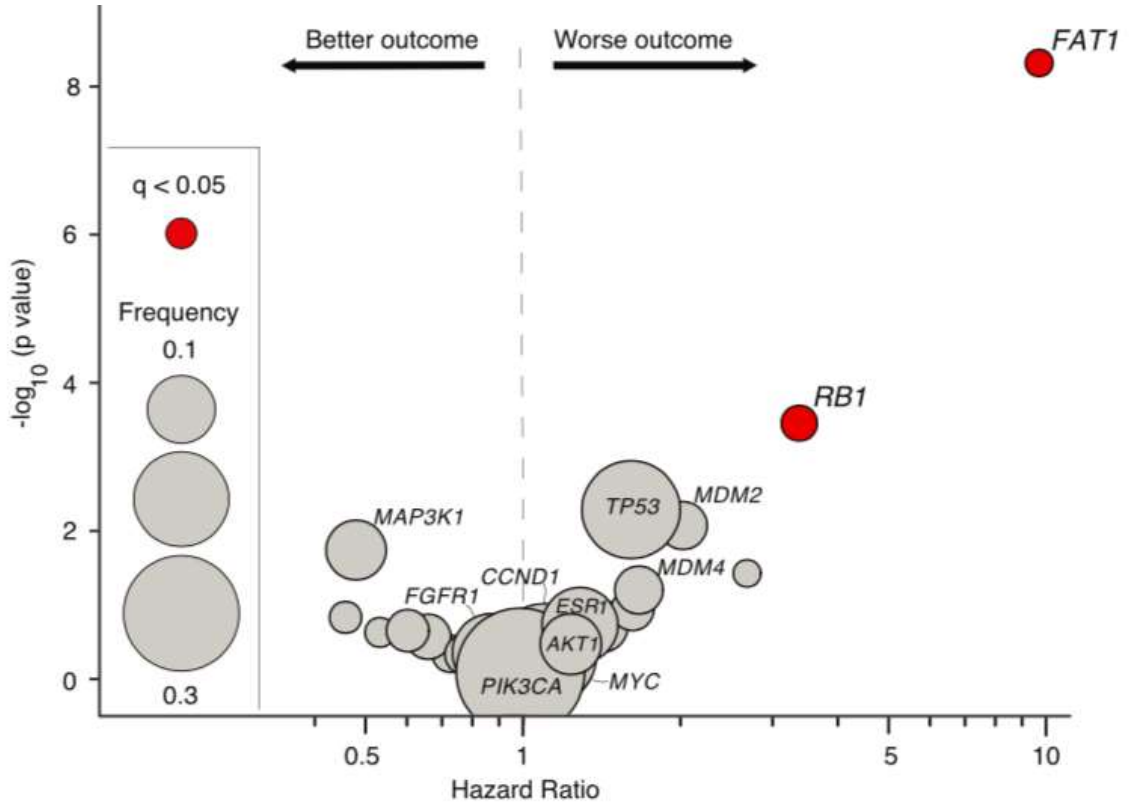
R. Condorelli[1†], L. Spring[2†], J. O'Shaughnessy[3,4], L. Lacroix[1], C. Bailleux[1], V. Scott[1], J. Dubois[2], R. J. Nagy[5], R. B. Lanman[5], A. J. Iafrate[2], F. Andre[1†] & A. Bardia[2*,†]

Patients and methods: We identified patients who had pre- and post-genotyping in tissue and peripheral blood samples after receiving CDK 4/6 inhibitors. Genotyping was carried out in tumor tissue or blood collected before start of CDK 4/6 inhibitor and after disease progression on CDK 4/6 inhibitor, covering more than 90% of the coding region in *RB1*.

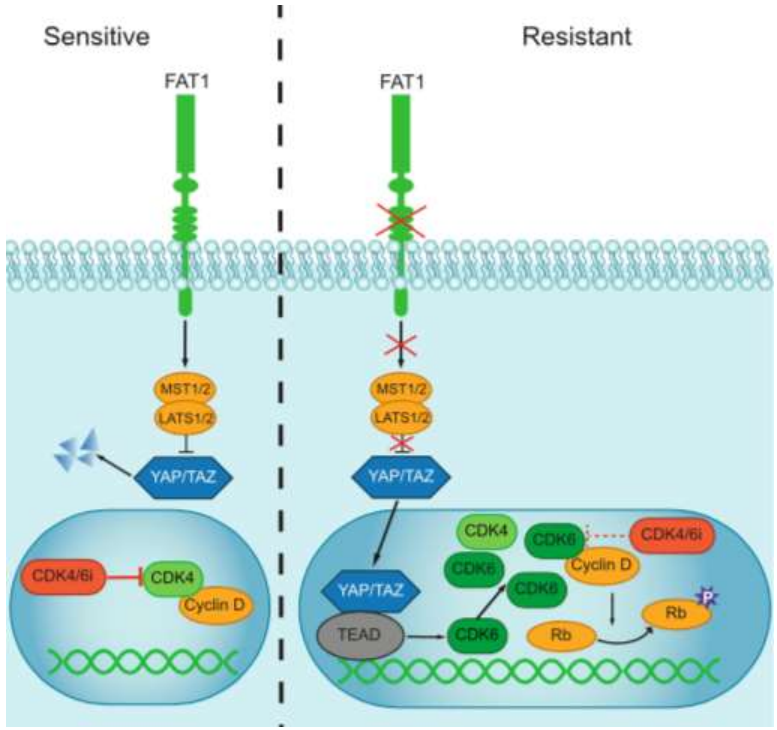
Results: We identified detectable acquired *RB1* mutations in circulating tumor DNA (ctDNA) after exposure to CDK4/6 inhibitor (palbociclib, palbociclib, ribociclib) for 5, 8, and 13 months, respectively, in three patients. The *RB1* mutations included substitution in donor splicing site of exon 8 of the *RB1* gene in patient #1; substitution in donor splicing site of exon 22 of *RB1* gene, exon 19 deletion, exon 3 insertion in patient #2; and *RB1* exon 16 H483Y mutation in patient #3. None of these *RB1* mutations were present in the pre-CDK 4/6 specimen highlighting these molecular alterations, which lead to functional loss of Rb1, likely emerged under selective pressure from the CDK4/6 inhibitor potentially confering therapeutic resistance.

Conclusion: This is the first clinical report to describe the emergence of somatic *RB1* mutations after exposure to palbociclib or ribociclib, in patients with metastatic breast cancer. Further research is needed to validate these findings, identify how these mutations temporally emerge under selective pressure of CDK 4/6 inhibitor, and develop rational therapeutic strategies.

FAT1 or RB1 loss is associated with clinical resistance to CDK4/6i

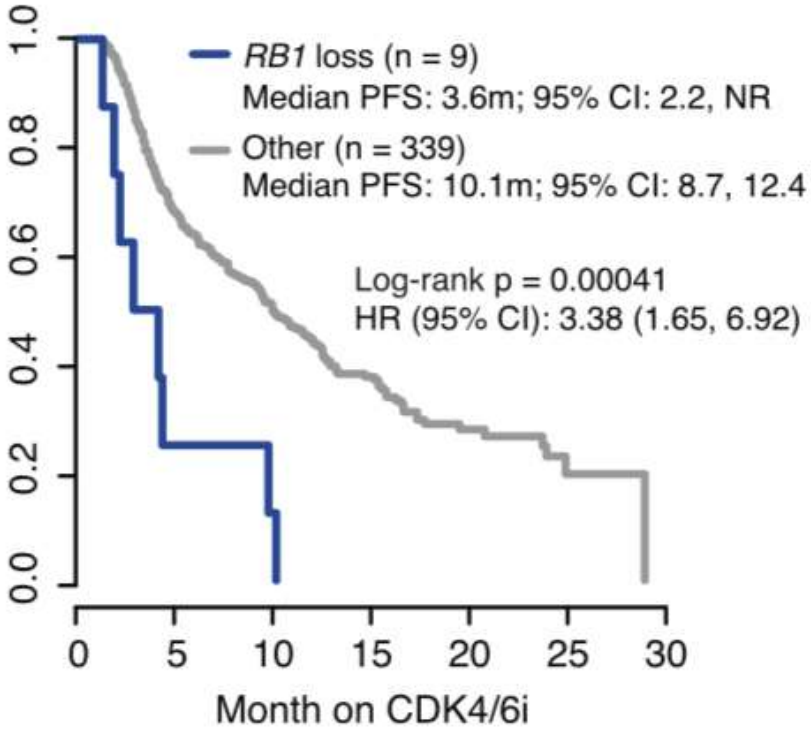


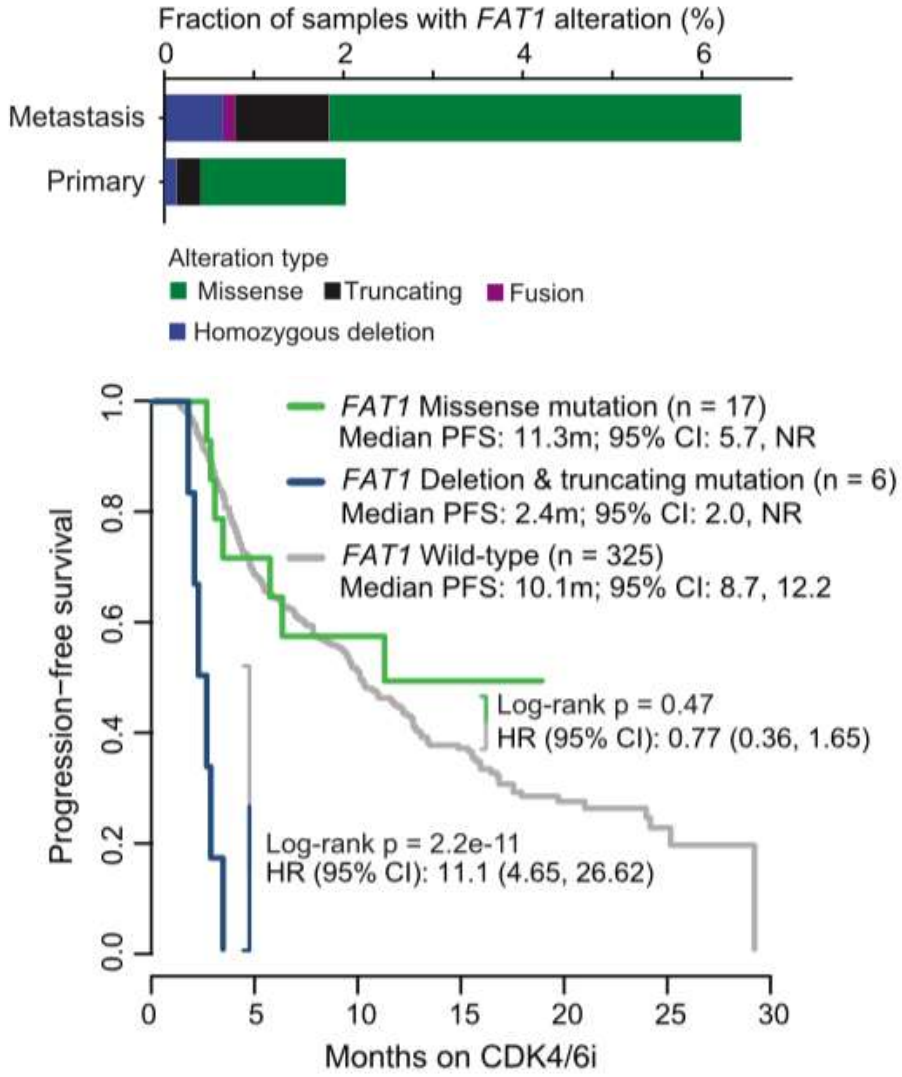
Genomic analyses of 348 pts with ER+ mBC treated with CDK4/6i



Li et al. *Cancer Cell* 2018

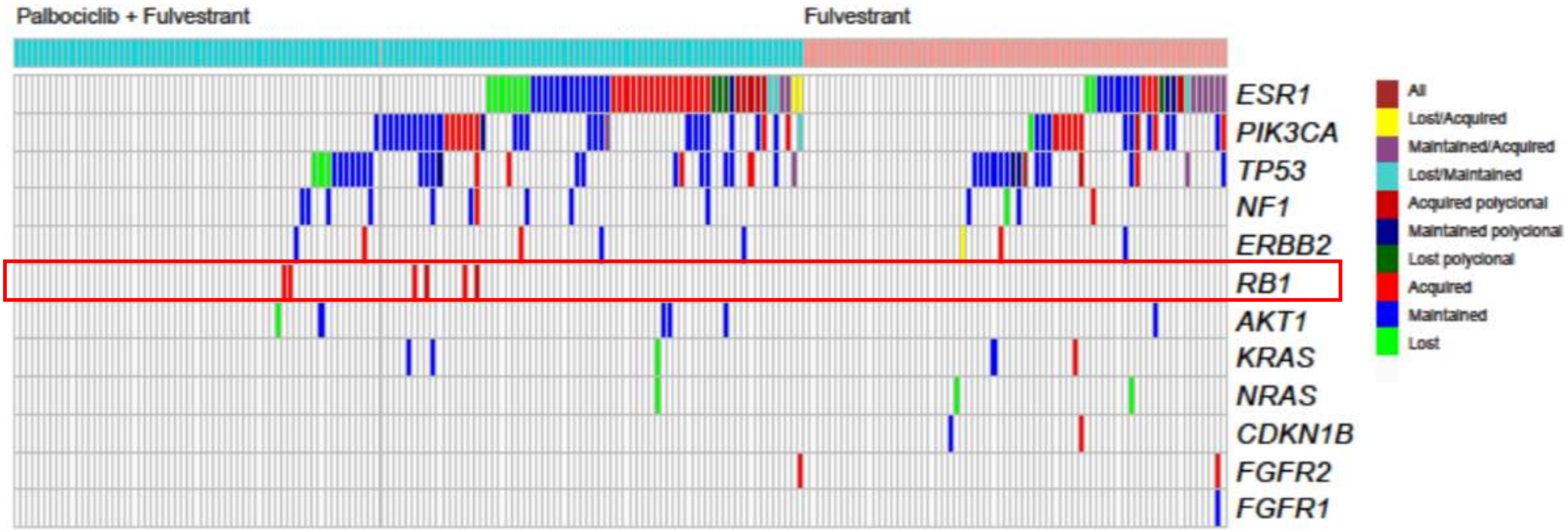
FAT1 or RB1 loss is associated with clinical resistance to CDK4/6i





Li et al. *Cancer Cell* 2018

The genetic landscape and clonal evolution of BC resistance to palbociclib plus fulvestrant in the

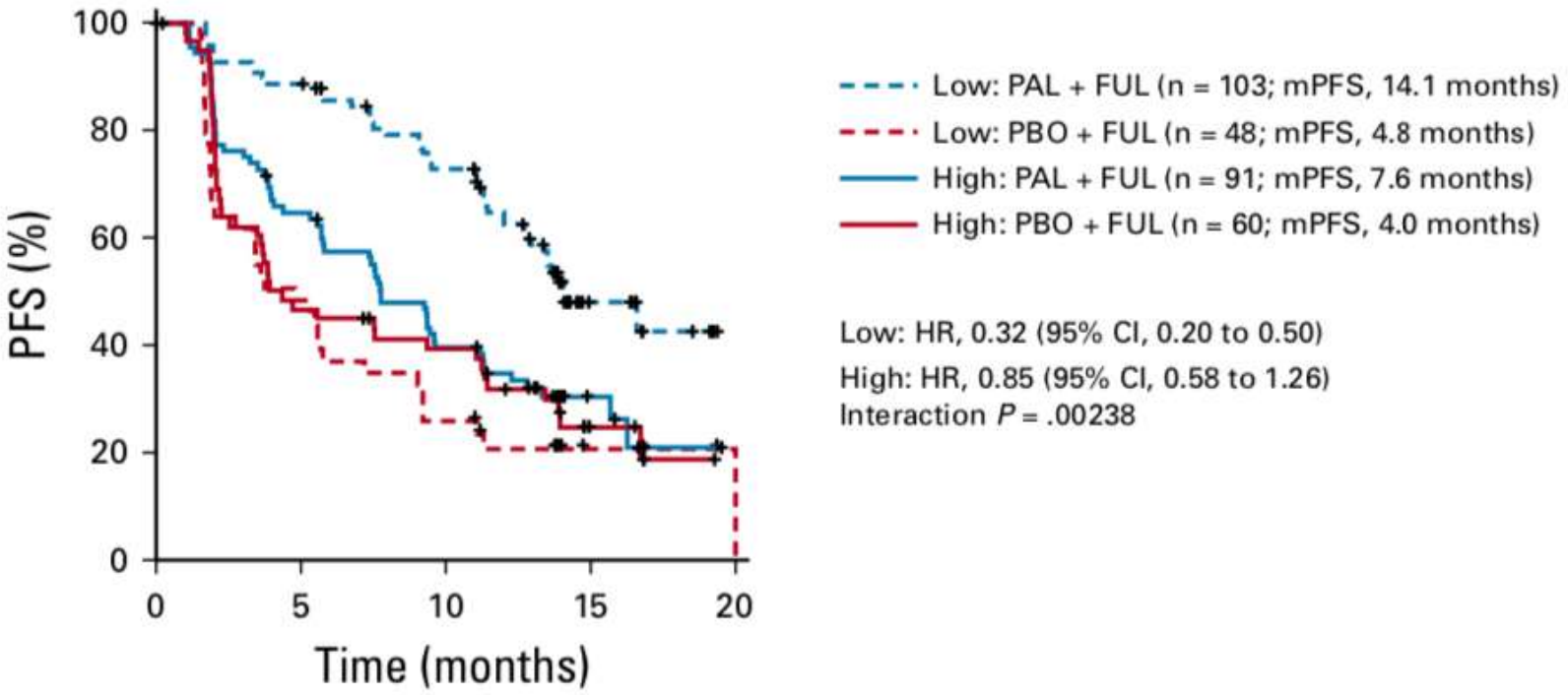


Acquired RB1 aberrations in 4.7% pts, only in the palbo arm

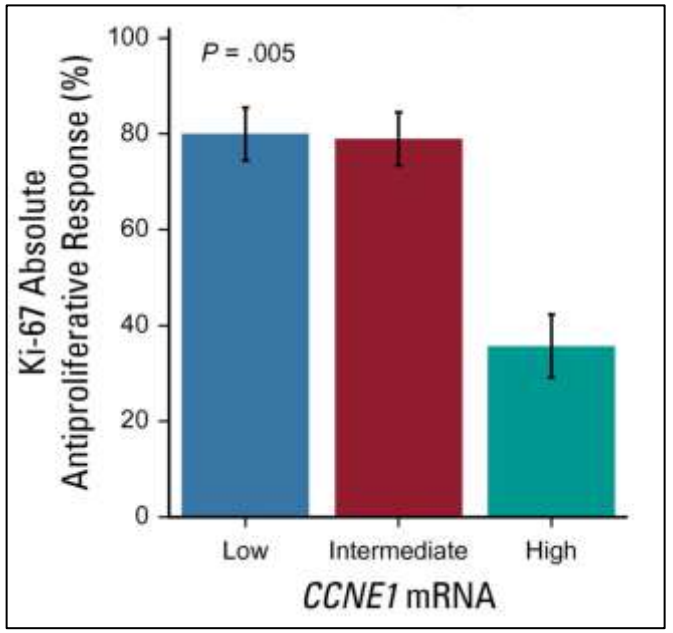
O'Leary et al. *Cancer Discov* 2018

Cyclin E1 expression and palbociclib efficacy

PALOMA-3



POP trial

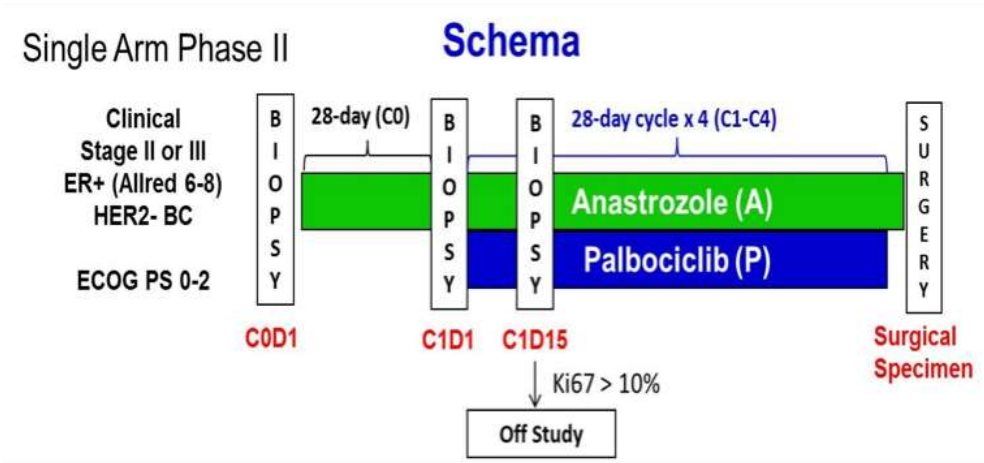


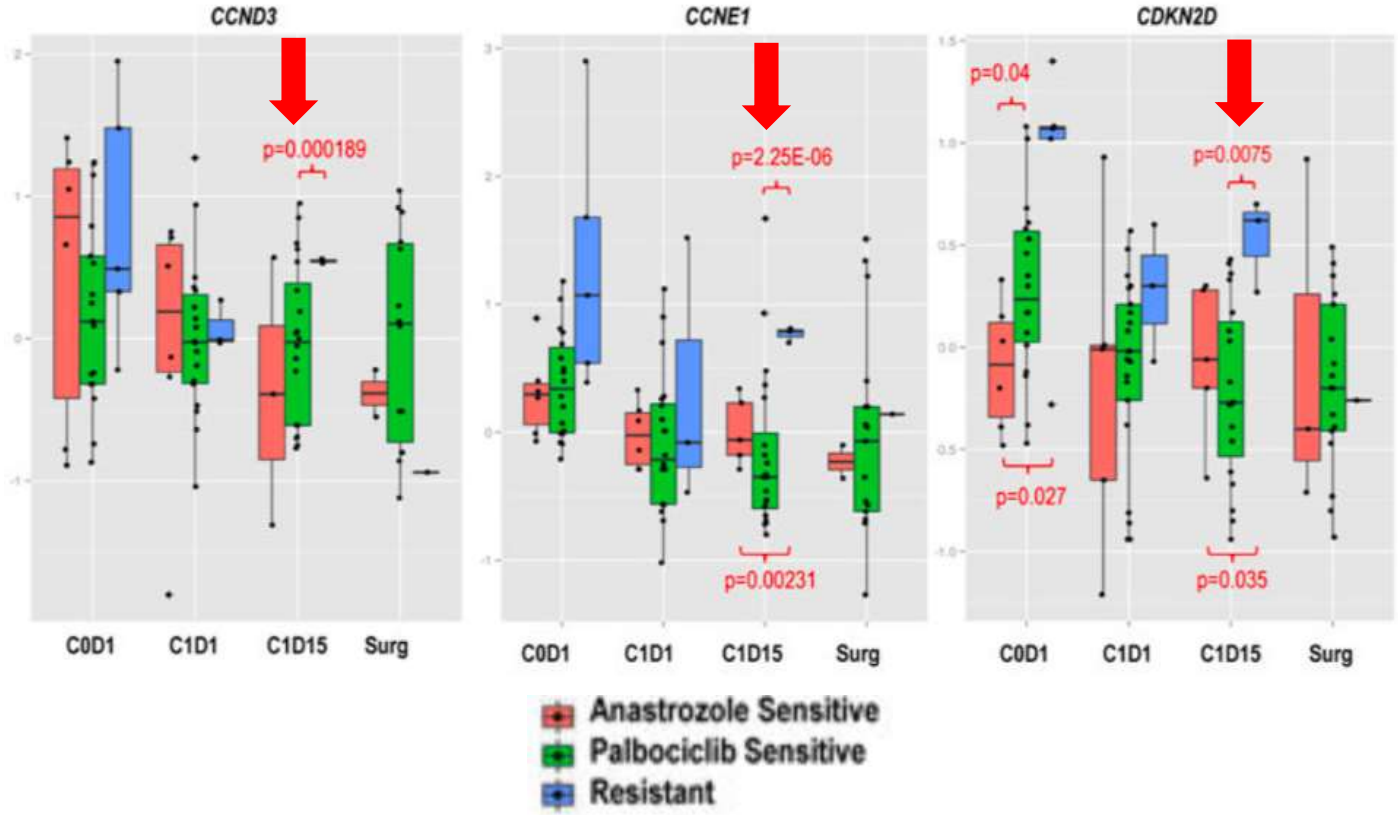
CCNE1 mRNA expression is predictive of palbociclib efficacy (when assessed in metastatic tissues)
High CCNE1 mRNA expression was associated with poor antiproliferative activity of palbociclib in the POP trial.

Turner et al. *JCO* 2019

E2F targets expression and palbociclib efficacy

NeoPalAna trial





Treatment resistance was associated with **non-luminal subtype** and persistent on-treatment **expression of E2F targets** including CCND3, CCNE1, CDKN2D.

Ma et al. *Clin Cancer Res* 2017

Conclusions

1) The CDK4/6 pathway has a complex biology

2) Combinatorial strategies are needed to overcome early adaptation to CDK4/6i

3) Despite preclinical evidence of several mechanisms of *de novo* or acquired resistance, there is no biomarker clinically useful to rationally allocate patients to these agents