# Advances in CDK 4/6 inhibitors in the treatment of HR+ HER2- metastatic breast cancer

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# Disclosures

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# The present and future of CDK 4/6 inhibitors

- What we know
- What we don’t know
- What the future holds

# Chemotherapy better than Endocrine Therapy in First-line setting?

**Figure 2** HR for PFS/TTP
All treatments vs anastrozole

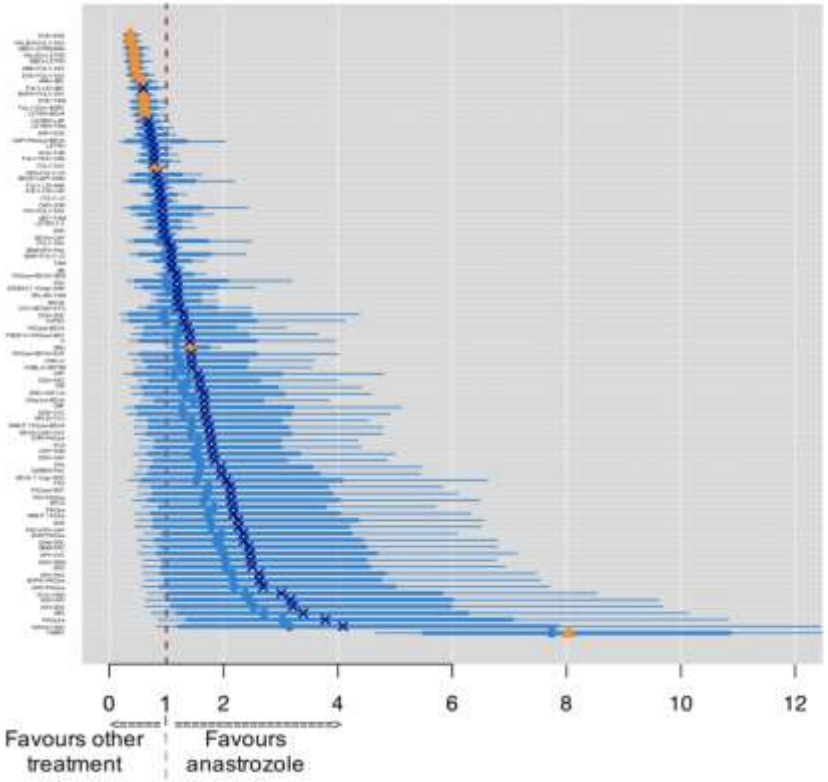
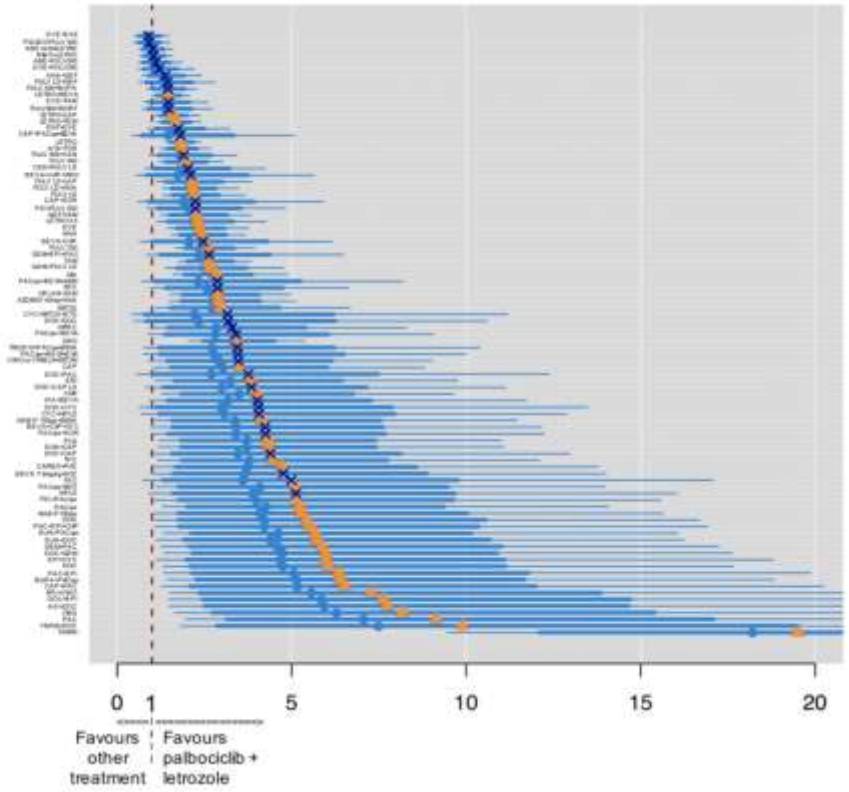



**Figure 3** HR for PFS/TTP
All treatments vs palbociclib+letrozole




Schettini. SABCS 2018

# CDK 4/6 inhibitors: FDA-approved indications 2018

| | Dose | Schedule | Indications: |
|---|---|---|---|
| **Palbociclib** (Ibrance, Pfizer) | 125 mg daily | 3 weeks on/1 week off | • **First line** with AI<br>• **Progressing after ET**, with fulvestrant |
| **Ribociclib** (Kisqali, Novartis) | 600 mg daily | 3 weeks on/1 week off | • **First line** with AI and Fulvestrant |
| **Abemaciclib** (Verzenio, Lilly) | 150 or 200 mg twice daily | **Continuous** | • **First line** with AI<br>• **Progressing after ET,** with fulvestrant<br>• **Monotherapy after progression** on ET and CT |

# Benefit of CDK 4/6 in First line setting

| Study/Arms | N | Med FU | Median PFS (months) Plac | Median PFS (months) CDK4/6i | HR 95% CI |
|---|---|---|---|---|---|
| PALOMA-2 Letrozole +/- Palbociclib | 666 | 37.6 | 14.5 | 27.6 | 0.56 0.46-0.69 |
| MONALEESA-2 Letrozole +/- Ribociclib | 668 | 26.4 | 16 | 25.3 | 0.57 0.46-0.70 |
| MONARCH-3 NS-AIs +/- Abemaciclib | 493 | 26.7 | 14.7 | 28.1 | 0.54 0.42-0.69 |
| MONALEESA-3 Fulvestrant +/- Ribociclib | 367 | 20.4 | 18.3 | NR | 0.58 0.415-0.802 |

*Finn RS, NEJM. 2016; Updated SABCS 2017; Hortobagyi , Annals Onc, 2018;; Goetz MP, et al. AACR, 2018; Slamon DJ, ASCO, 2018 Abs 1000*

# Benefit of CDK 4/6 in Second line setting

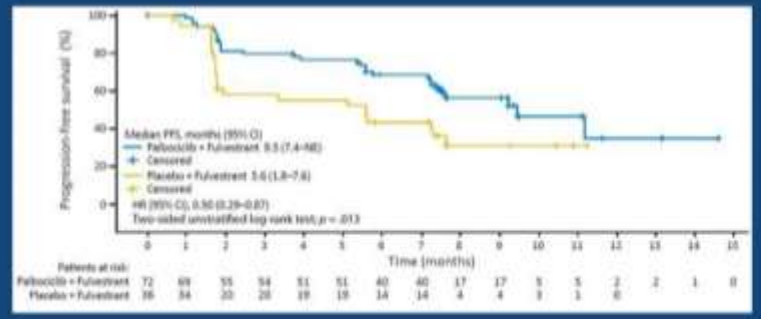
| Study/Arms | N | Med FU (mos) | Median PFS (months) Plac | Median PFS (months) CDK 4/6i | HR 95% CI |
|---|---|---|---|---|---|
| PALOMA 3 Fulvestrant +/- Palbociclib | 521 | 15 | 4.6 | 11.2 | 0.50 0.40–0.62 |
| MONARCH 2 Fulvestrant +/- Abemaciclib | 669 | 19.5 | 9.3 | 16.4 | 0.55 0.45-0.68 |
| MONALEESA-3 Fulvestrant +/- Ribociclib | 345 | 20.4 | 9.1 | 14.6 | 0.57 0.42 – 0.74 |

*Turner NC, NEJM. 2015; Updated ASCO 2016; Sledge, JCO. 2017;, Slamon, DJ, ASCO, 2018, abs 1000*

# Active in premenopausal patients, regardless of endocrine therapy used

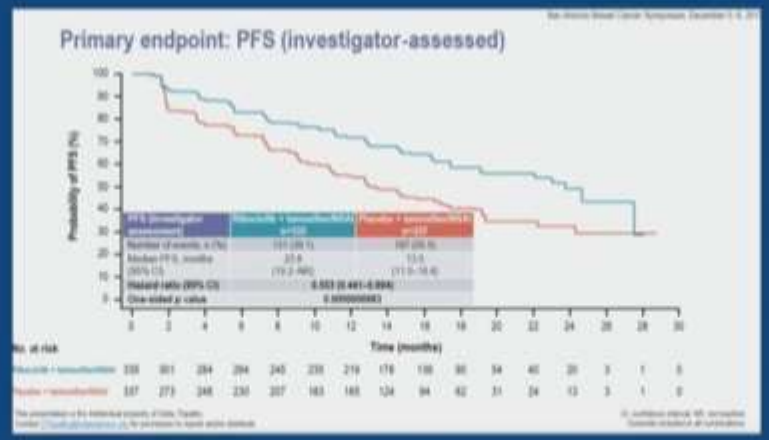
## PALOMA-3

- N=106
- Fulvestrant + goserelin
- HR 0.50 p=0.013



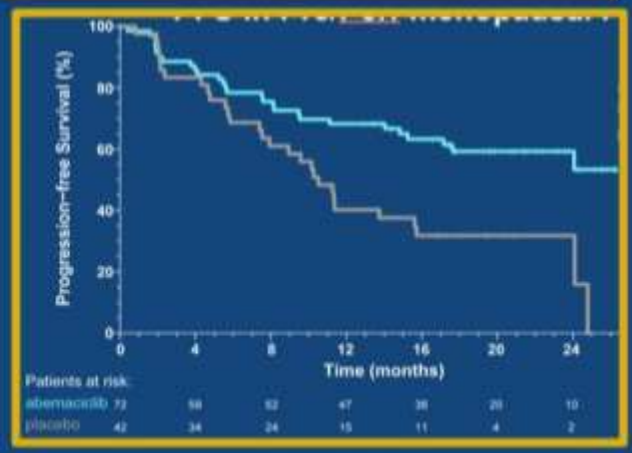

## MONALEESA-7

- N=335
- Tamoxifen or NSAI+ goserelin
- HR 0.55, p=1x10-9




## MONARCH-2

- N=114
- Fulvestrant + GnRH
- HR 0.45, p=0.002




*Loibl, Oncologist, 2017; Tripathy D, et al. SABCS, December 2017. Abstract GS2-05; Neven, ASCO, 2018, Abs 1002*

# Heath Related Quality of Life - MONARCH 3

**Figure 1a: EORTC QLQ-C30 Abemaciclib vs Placebo Longitudinal Mean Changes from Baseline Treatment Group Difference: Functional Scale Scores**

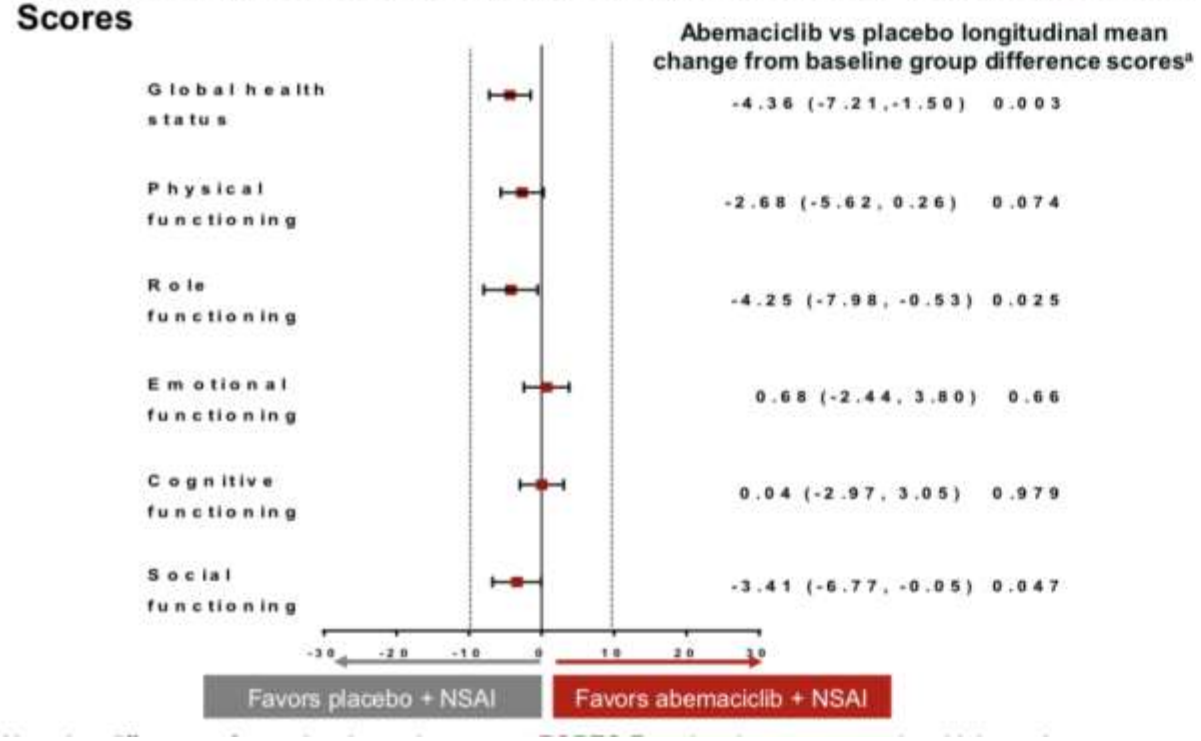
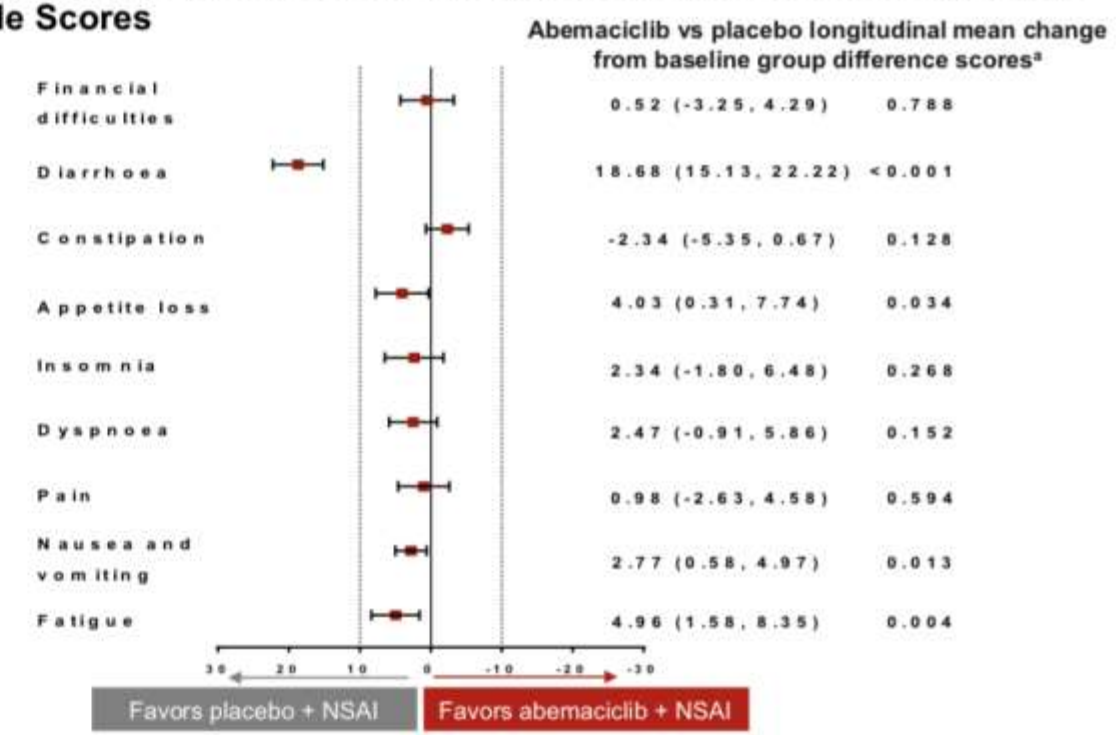


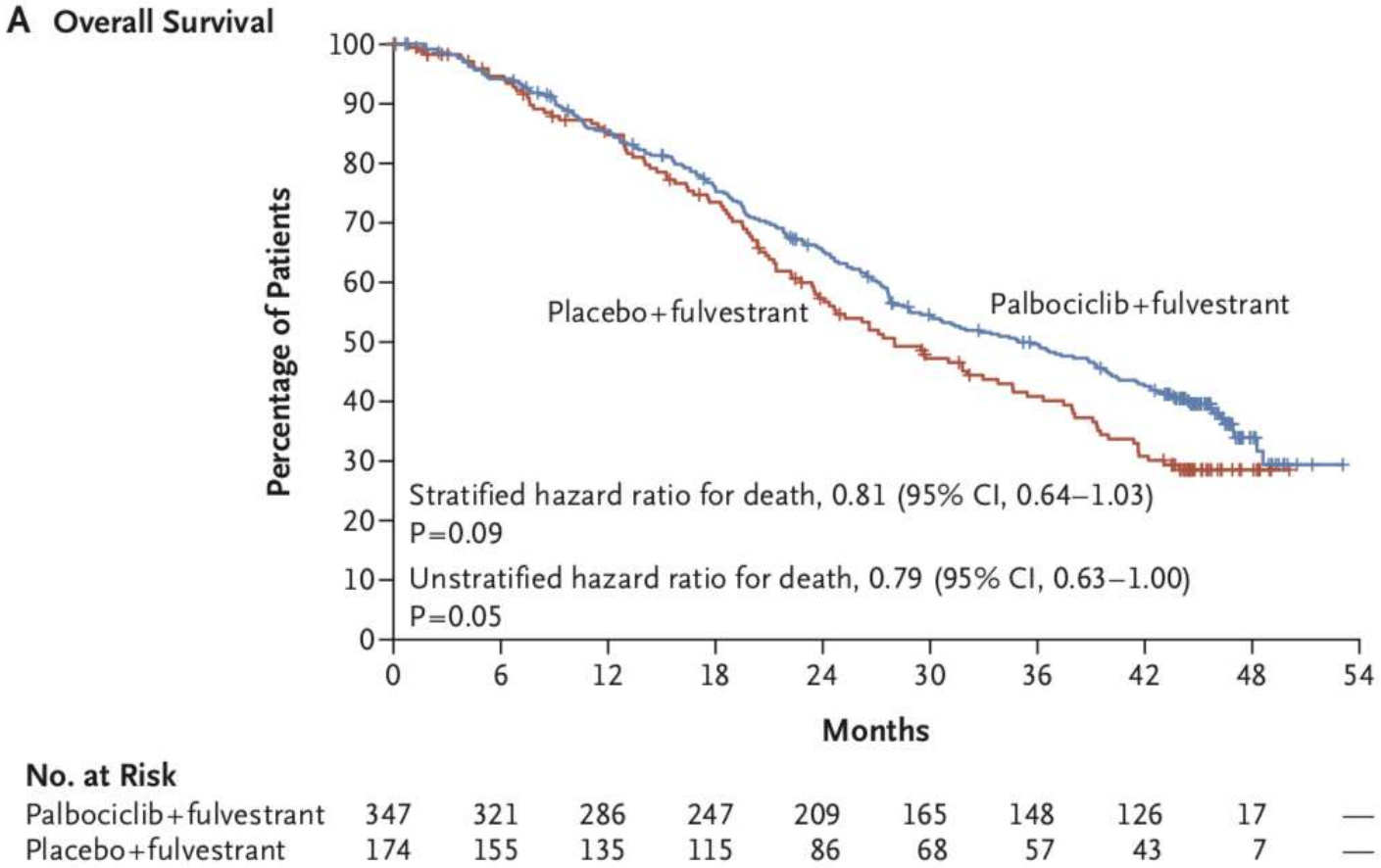

**Figure 1b: EORTC QLQ-C30 Abemaciclib vs Placebo Longitudinal Mean Changes from Baseline Treatment Group Difference: Symptom Scale Scores**




Reduction in PAIN scores – PALOMA 2 and MONALEESA 2

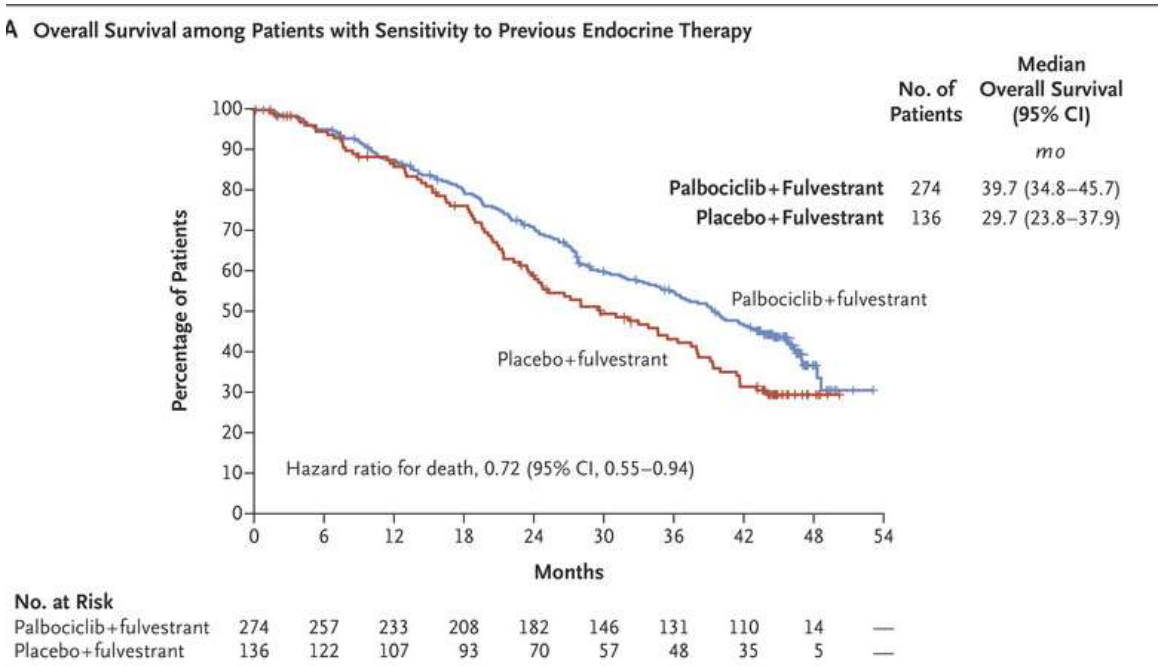
Goetz. SABCS 2018

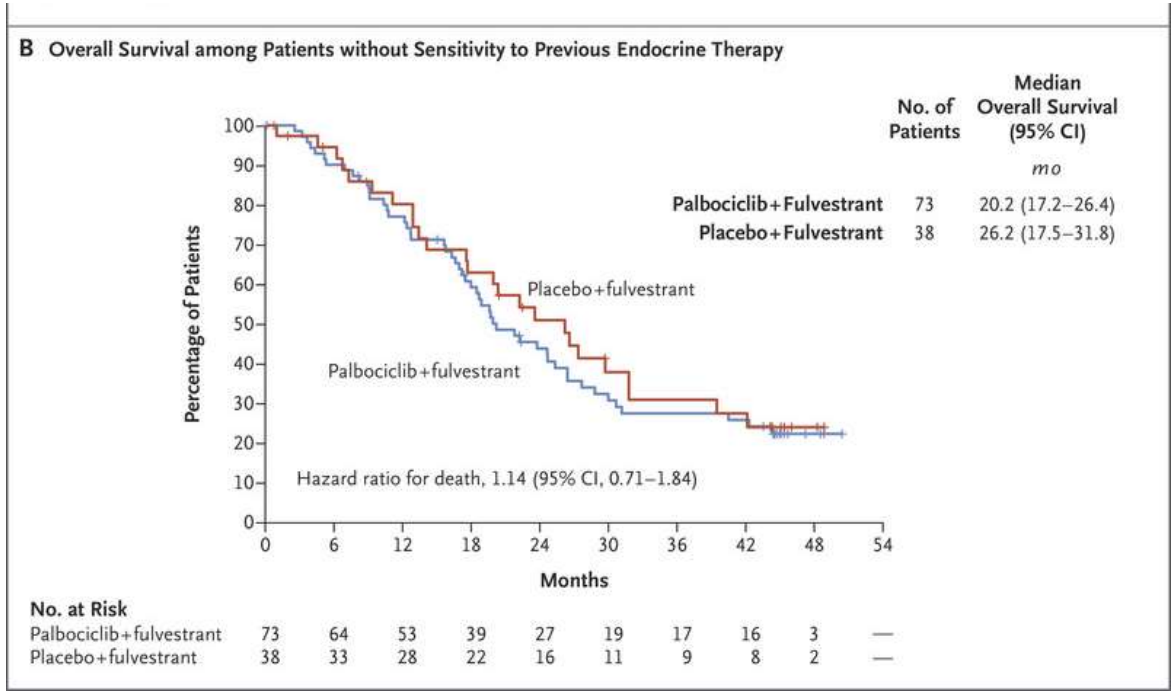
# Overall Survival with Palbociclib – PALOMA 3




| | No. of Patients | Median Overall Survival (95% CI) |
|---|---|---|
| | | *mo* |
| **Palbociclib+ Fulvestrant** | 347 | 34.9 (28.8–40.0) |
| **Placebo+ Fulvestrant** | 174 | 28.0 (23.6–34.6) |

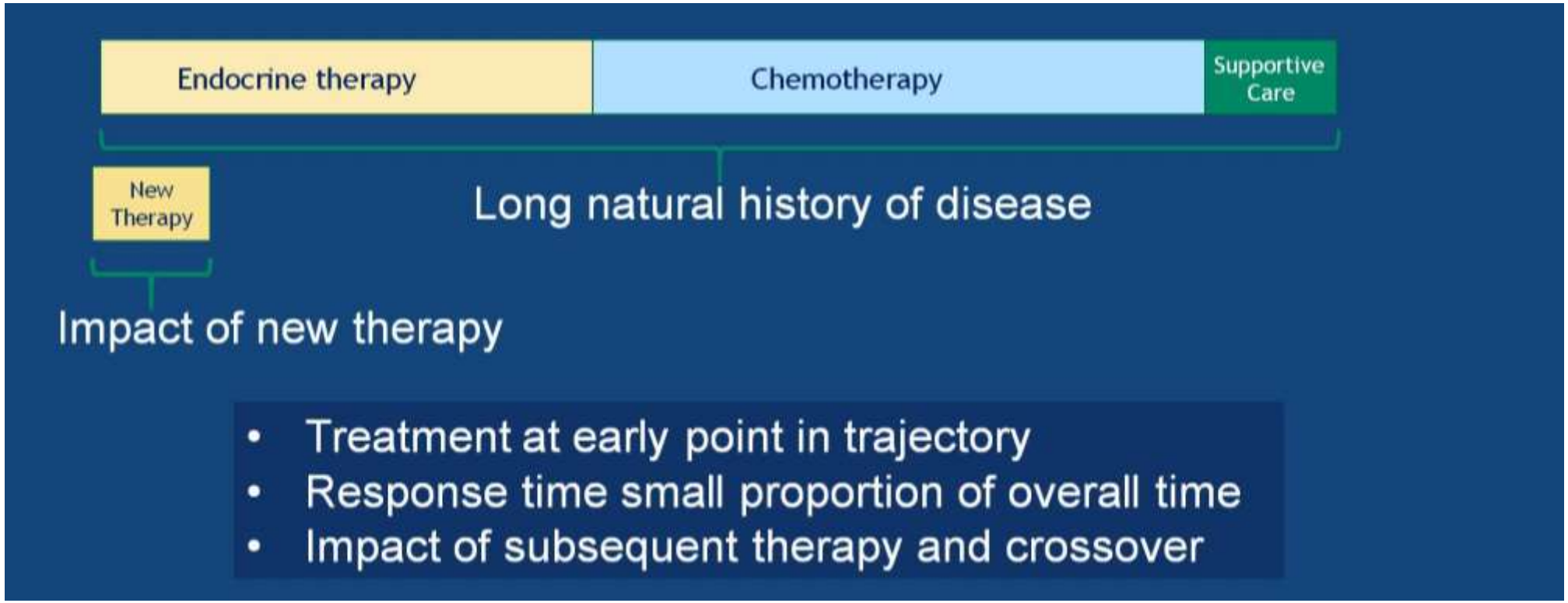
# Overall Survival with Palbociclib by Sensitivity




Turner. N Engl J Med 2018;379:1926-36

# Difficult to demonstrate overall survival benefit in ER+, metastatic breast cancer



# Toxicity differences between agents: Grade 3/4

| | Palbociclib | Ribociclib | Abemaciclib |
|---|---|---|---|
| Neutropenia | ✓✓✓ | ✓✓✓ | ✓✓ |
| Anemia | ✓✓ | ✓✓ | ✓✓ |
| Thrombocytopenia | ✓ | | |
| Fatigue | ✓ | ✓ | ✓ |
| Diarrhea | ✓ | ✓ | ✓✓ |
| Nausea | | | ✓ |
| QTc prolongation | | ✓ | |

**Are differences due to drug, schedule or population?**

# What we don’t know?

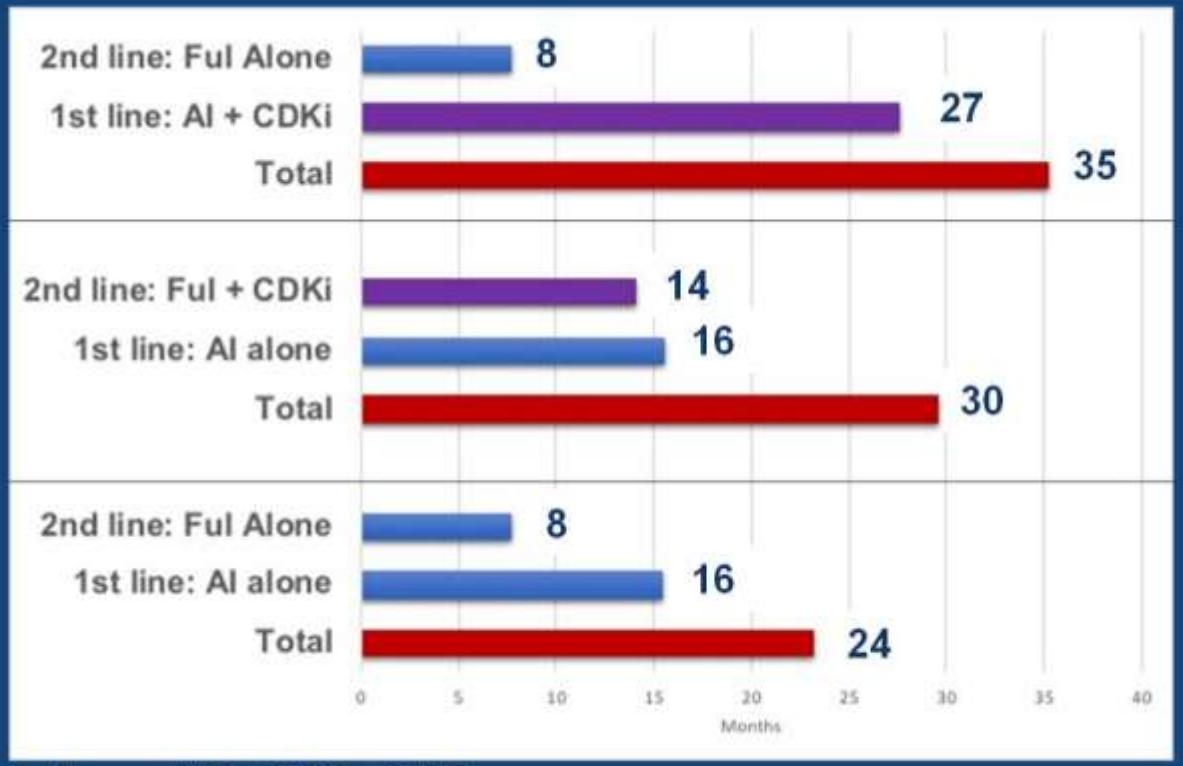
- When to best integrate into the therapeutic plan?
- Which tumors biologically most likely to responde?
- Mechanism of resistance?
- What is next line post progression?

# When should we add CDK inhibitors to endocrine therapy?

**1st line CDK inhibitor: Total PFS 35 months**

**2nd line CDK inhibitor: Total PFS 30 months**

**No CDK inhibitor: Total PFS 24 months**



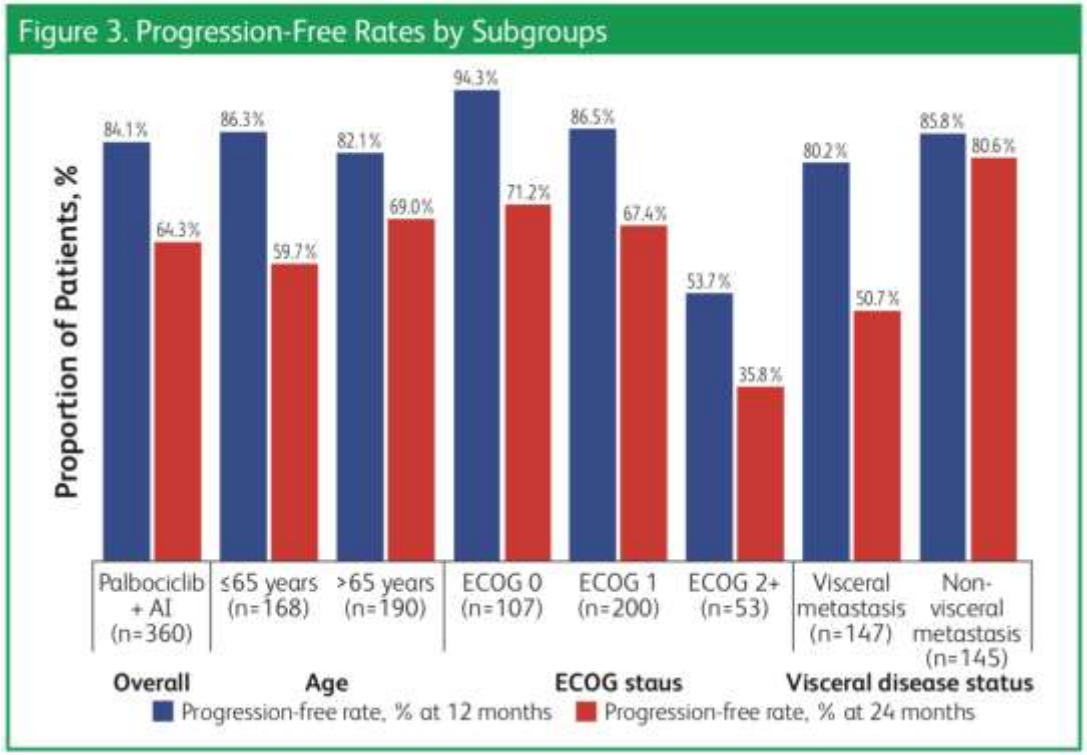

- Not crossover studies!

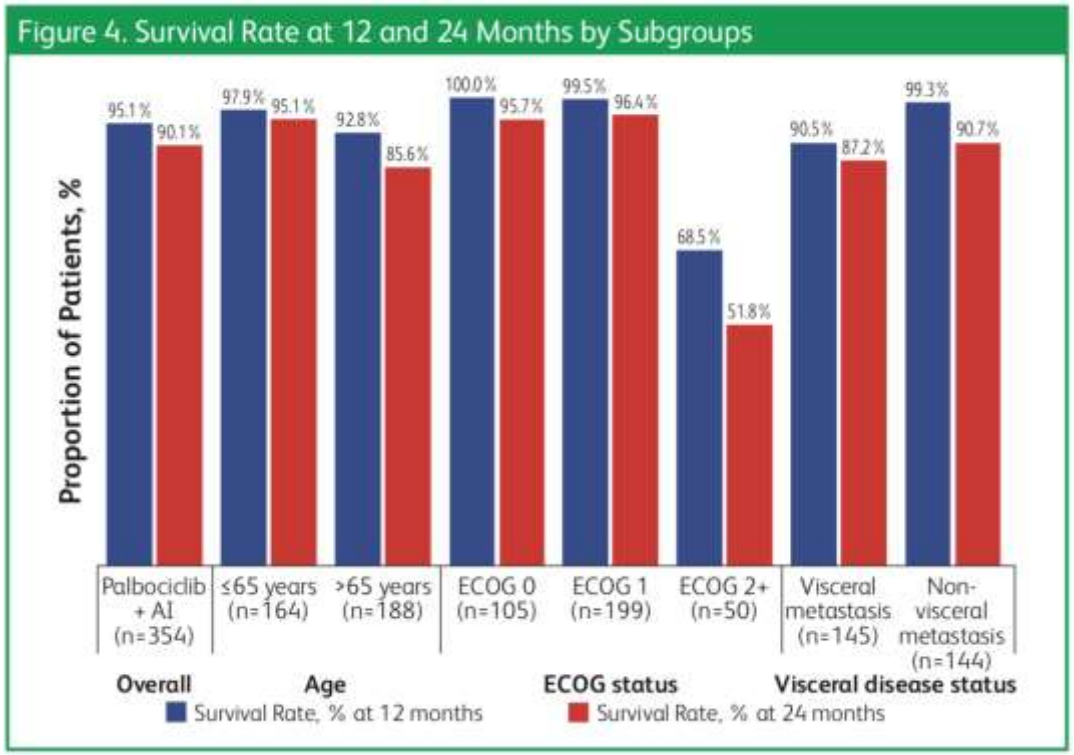
**Individual Considerations:**

- Desire for time without treatment change
- Toxicity
- Access
- Cost

*Adapted from Ingrid Mayer, MD, ASCO, 2017*

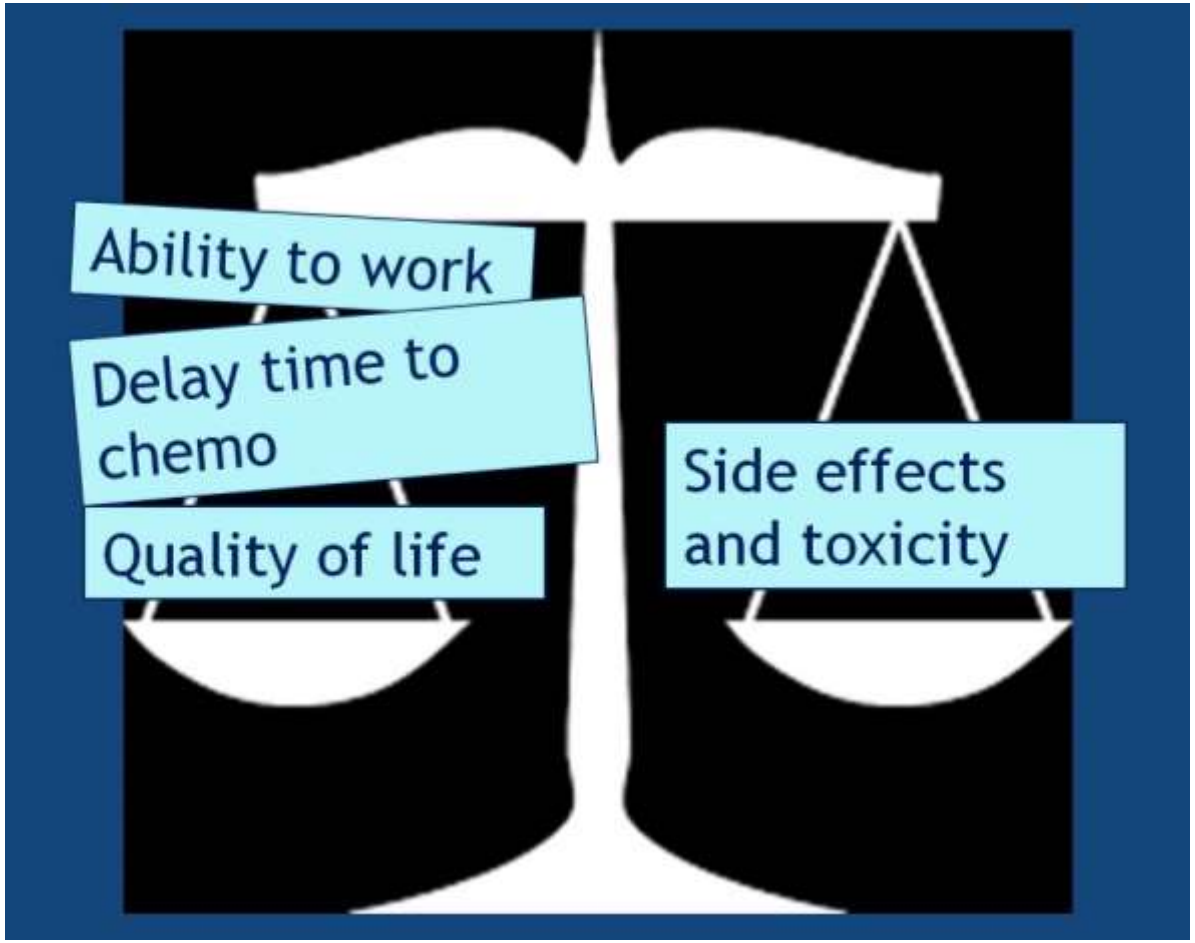
# Real World Data IRIS




Taylor-Stokes. P6-18-36 SABCS 2018

# What should we consider when indicating a CDK?



# Is it Cost Effective – OS

| Regimen | Lifetime costs ($) | Life expectancy (years) | Health benefits (QALYs) | ICER ($/QALY) |
|---|---|---|---|---|
| Letrozole | 170,829 | 3.47 | 2.08 | – |
| Palbociclib + letrozole (base price) | 475,339 | 3.77 | 2.56 | 634,396 |
| 25% price reduction | 385,444 | | | 447,115 |
| 50% price reduction | 295,549 | | | 259,833 |
| 75% price reduction | 205,653 | | | 72,550 |
| Ribociclib + letrozole (base price) | 549,164 | 4.27 | 2.94 | 439,924 |
| 25% price reduction | 440,628 | | | 313,720 |
| 50% price reduction | 332,093 | | | 187,516 |
| 75% price reduction | 223,558 | | | 61,313 |

*QALY* Quality-adjusted life year, *ICER* Incremental cost-effectiveness ratio, measured in cost per QALY gained, relative to letrozole

All costs and QALYs are discounted at a 3% annual rate

Zhang. Breast Can Res Treat 2019

# Can biomarkers help us to optimize therapy?

- Biologic Responders
- Mechanism of resistance
- Therapeutic interventions at progression

# Biomarkers that have NOT identified responders:

- Cyclin D amplification (*CCDN1*)
- Loss of p16 (*INK4A or CDKN2A*)
- Protein levels of cyclin D/CDK4/6/Rb pathway
- Expression level of ER and/or PgR
- *PIK3CA* mutations (cfDNA)
- *ESR1* mutations (cfDNA) – note trend in MONALEESA-2 *(Hortobagyi, ASCO 2018, Abs 1026)*

*Finn, Lancet Oncol. 2015; Cristofanilli, Lancet Oncol. Fribbens, J Clin Oncol. 2016; Finn, ESMO 2016*

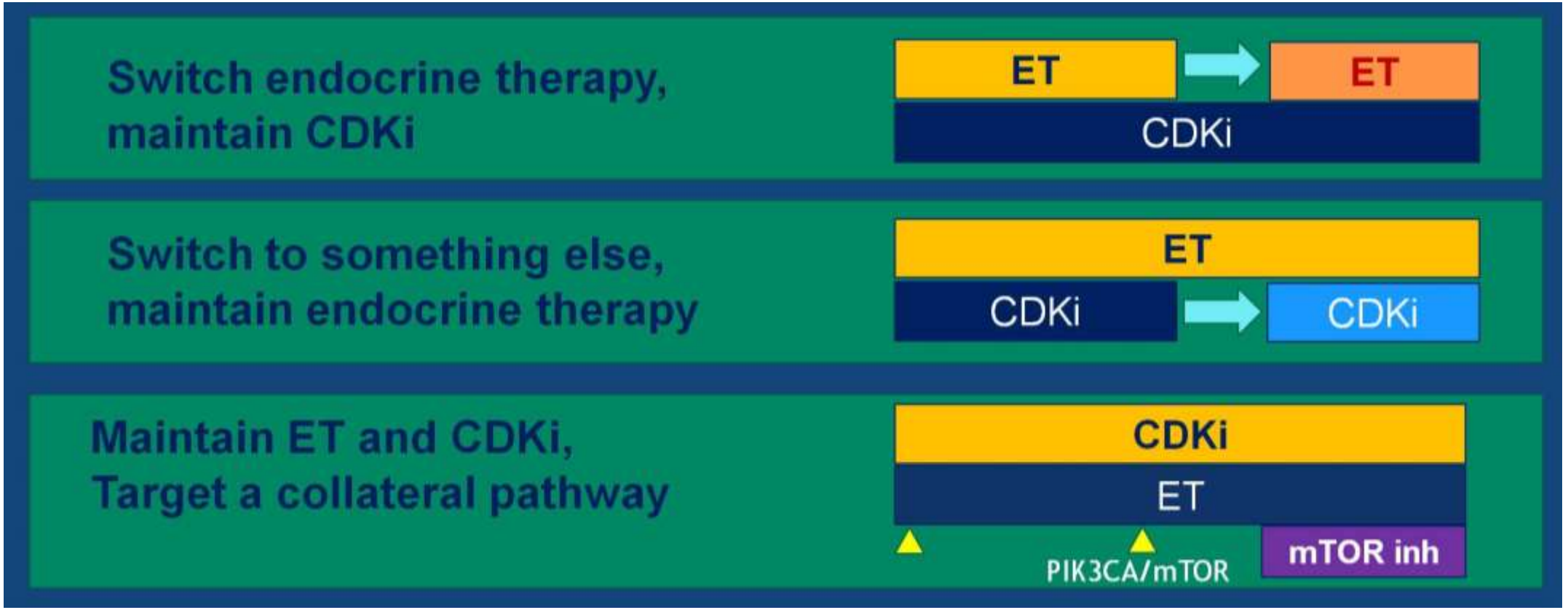
# Paired blood samples for circulating tumor DNA from PALOMA-3

- Pre- and post-treatment blood samples
- Targeted panel (n=193)
- Whole exome (n=14)

| Emergent Mutation | FUL | FUL + PAL |
|---|---|---|
| *RB* | 0% | **4.8%** |
| *PIK3CA* | **10.3%** | **8%** |
| *ESR1* | **14.7%** | **19.2%** |

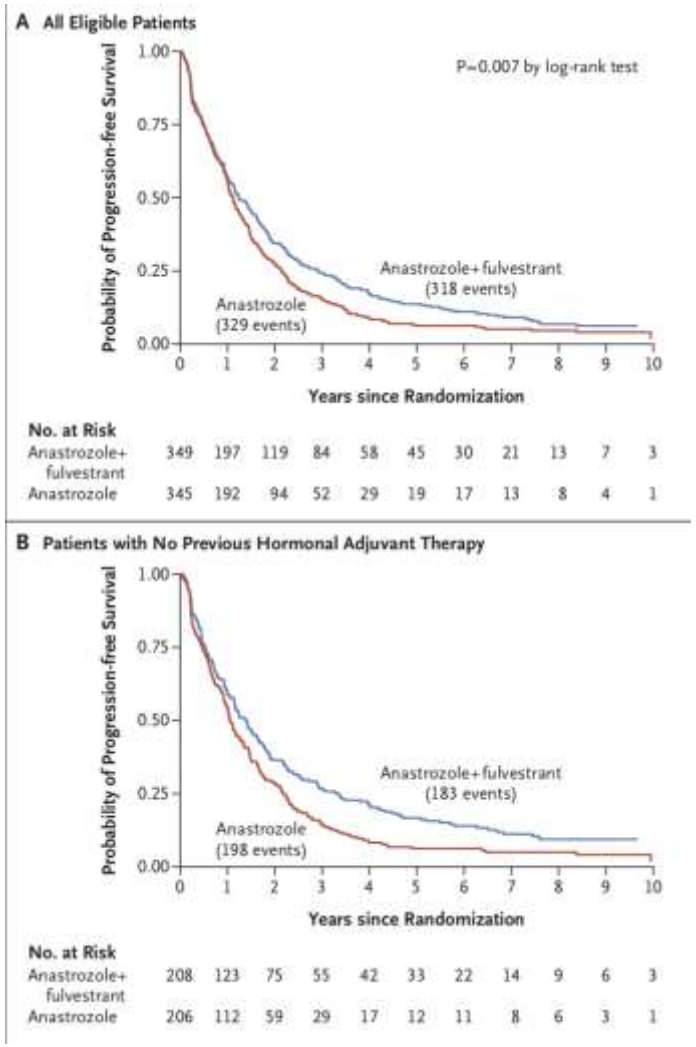
Turner et al, Abs 1001

# How could we manage our patients at progression?

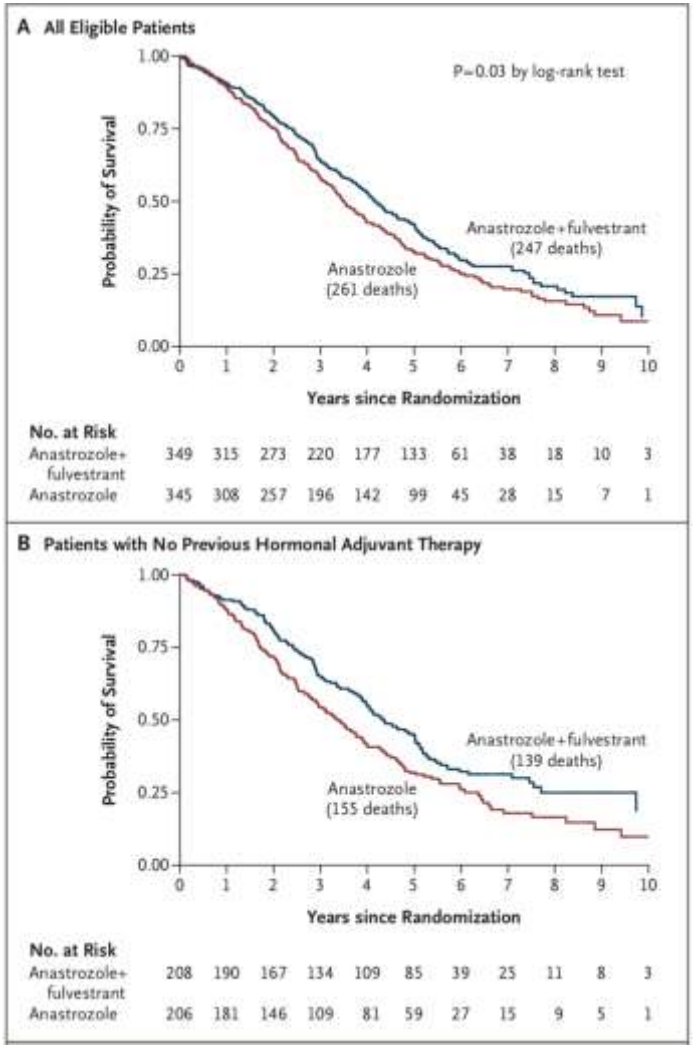


# Conclusion

- Consistent, clinically-meaningful improvements in PFS
- PFS benefit regardless of endocrine sensitivity, endocrine therapy partner, menopausal status
- Results of other trials to fully understand magnitude and nature of benefit in terms of OS
- Predictable, tolerable and manageable side effect profile




Median progression-free survival was 13.5 months in the anastrozole-alone group and 15.0 months in the combination-therapy group




median overall survival was 42.0 months in the anastrozole-alone group and 49.8 months in the combination-therapy group