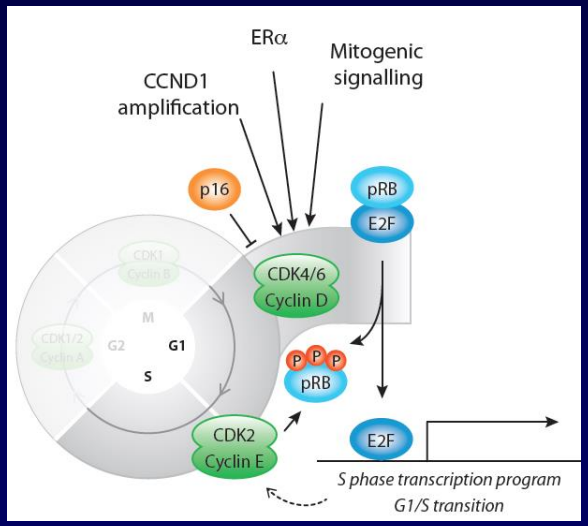
UCSF Helen Diller Family Comprehensive Cancer Center

# Leading the Way in the Treatment of HR+ HER2- MBC: CDK 4/6 Inhibitors in Clinical Practice

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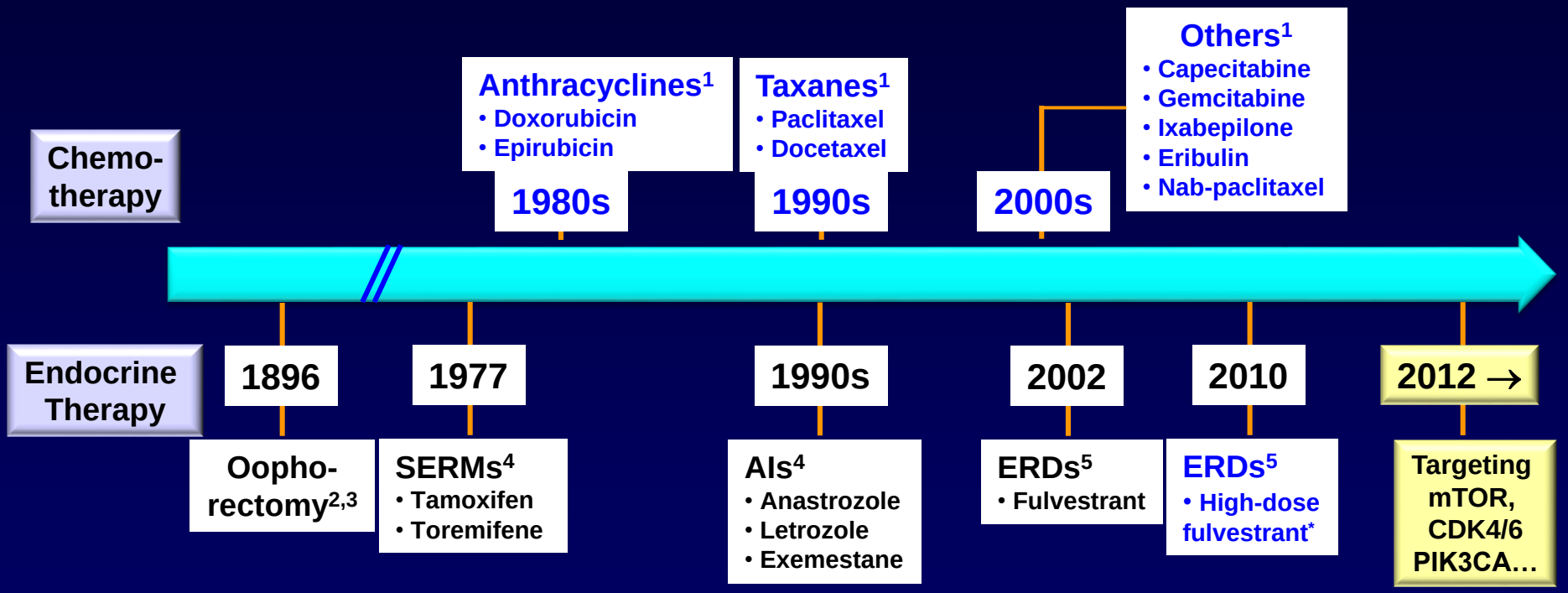
# Topics

- CDK 4/6 inhibitors have revolutionalized the treatment of HR+ MBC
- Is there an optimal sequence for hormone therapy?
- Should all patients receive CDK4/6 inhibitors in the first-line setting?
  - Understanding subsets and toxicity
  - Options for sequential therapy
- Understanding mechanisms of resistance

# Historical Timeline of Therapies for HR+ Advanced Breast Cancer




AI, aromatase inhibitor; ERDs, estrogen receptor downregulators; HR+; hormone-receptor positive; SERMs, selective estrogen receptor modulators

* Marginal improvement over lower dose fulvestrant.

**1. Advanced Breast Cancer Community Website. Available at: http://www.advancedbreastcancercommunity.org/treatment/drugs.html. Accessed April 20, 2015; 2. Beatson GT. *Lancet*. 1896;2:104-107; 3. Beatson GT. *Lancet*. 1896;2:162-165; 4. Cohen MH, et al. *Oncologist*. 2001;6(1):4-11; 5. Faslodex® [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2011.**

# HR+ MBC: Concordance Across International Guidelines

**ABC2 treatment guidelines for advanced breast cancer:[1,2]**

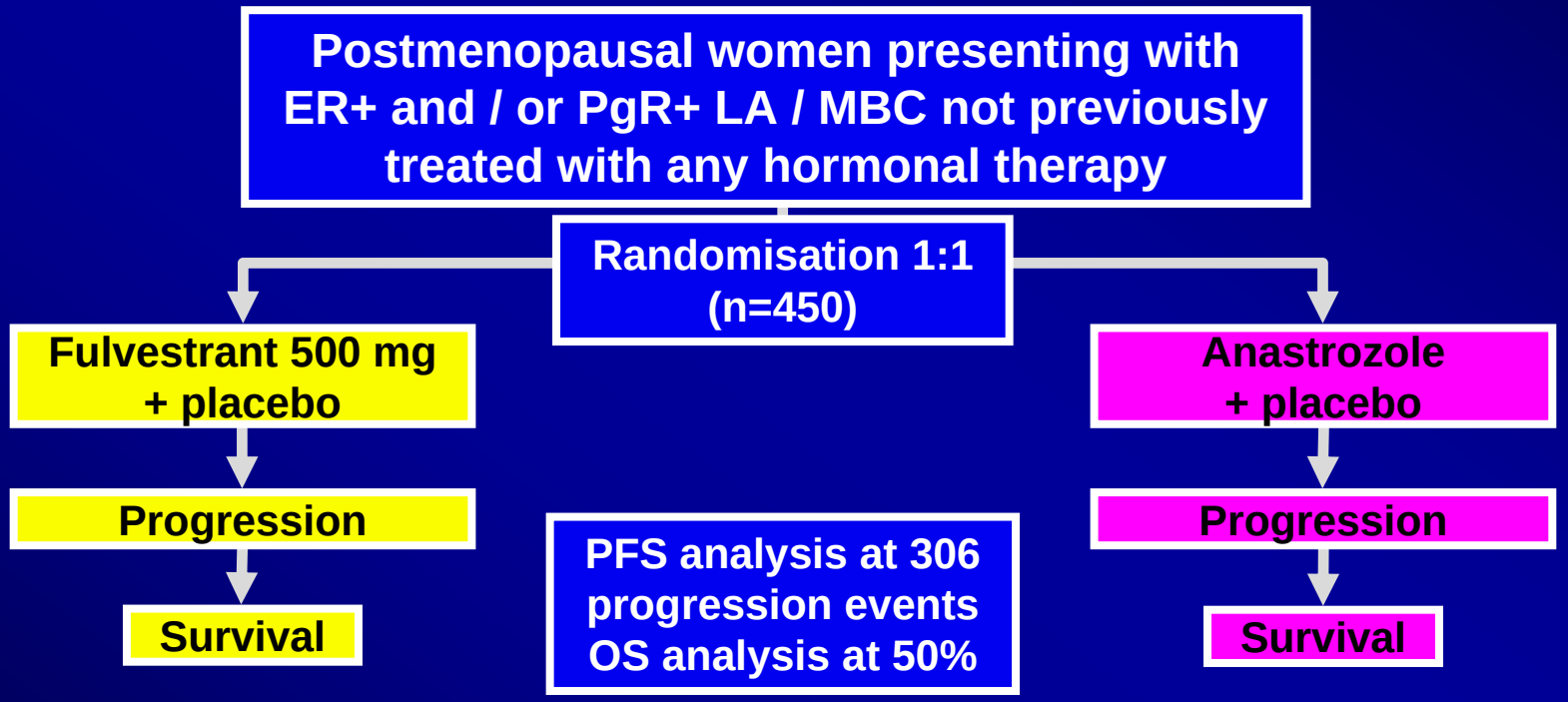
**Endocrine therapy (ET) is the preferred option for hormone receptor–positive disease**, even in the presence of visceral disease, unless there is concern or proof of endocrine resistance or rapidly progressive disease needing a fast response

**ASCO Guidelines for Metastatic HR+ Breast cancer[3]**

- Treatment should be administered until there is unequivocal evidence of disease progression as documented by imaging, clinical examination, or disease-related symptoms
- Use of combined endocrine therapy and chemotherapy is not recommended
- Patients should be encouraged to consider enrolling in clinical trials, including patients receiving treatment in first-line setting

1. Cardoso F, et al. *Ann Oncol 2014*. Wilcken N, et al. 2. *Cochrane Database Syst Rev*. 2003;2:CD002747. 3.Rugo HS, et al. *J Clin Oncol*. 2016;34:3069-3103.

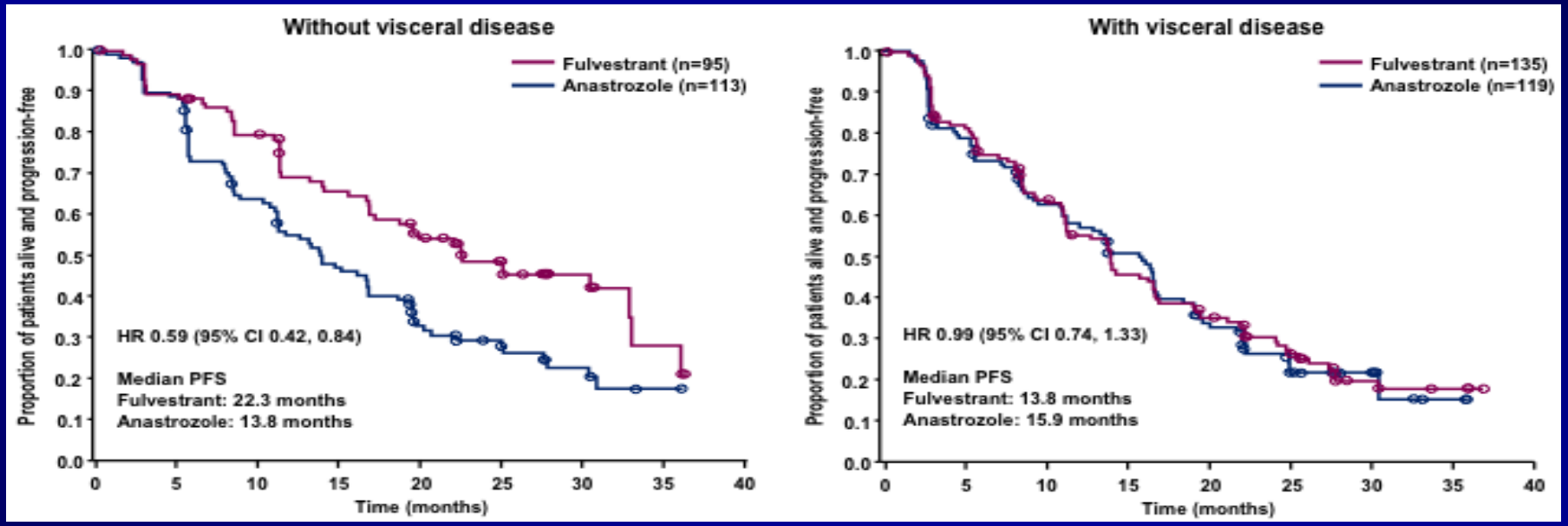
# What is the Best First-Line Hormone Therapy for Advanced Disease?: FALCON




One prior line of chemotherapy allowed. No HRT within 6 months
Stratification: measurable vs non-measurable disease; locally advanced vs metastatic

Robertson et al, Lancet 2016

# FALCON: PFS IN PATIENTS WITH OR WITHOUT VISCERAL DISEASE




Overall study results
**HR 0.797 (95% CI 0.637, 0.999); p=0.0486**

**Median PFS**
**Fulvestrant: 16.6 months**
**Anastrozole: 13.8 months**

Forest plot for subset analysis:

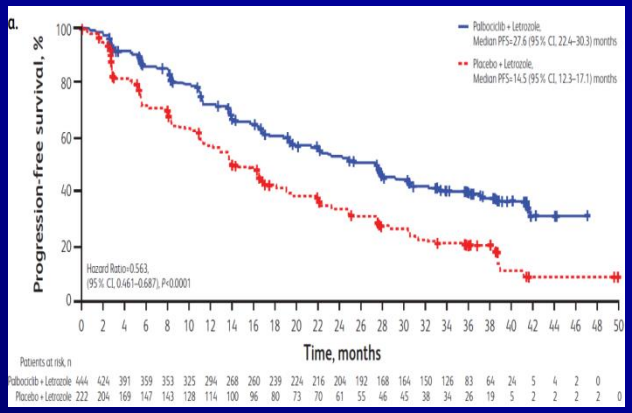
- No difference among predefined subsets EXCEPT visceral disease
  - HR 0.992 (visceral disease) vs 0.592 (non-visceral disease)
- No difference in OS to date

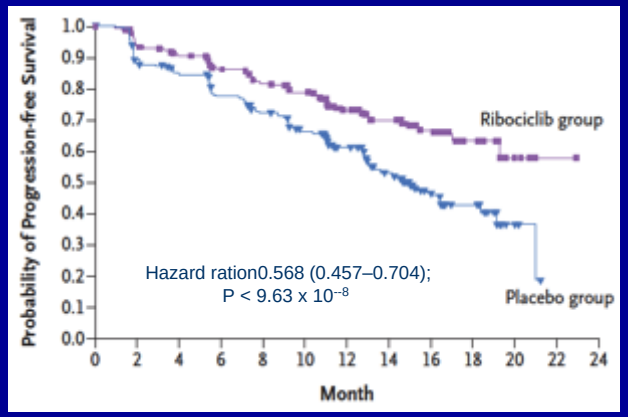
Post hoc interaction test p<0.01; A circle represents a censored observation

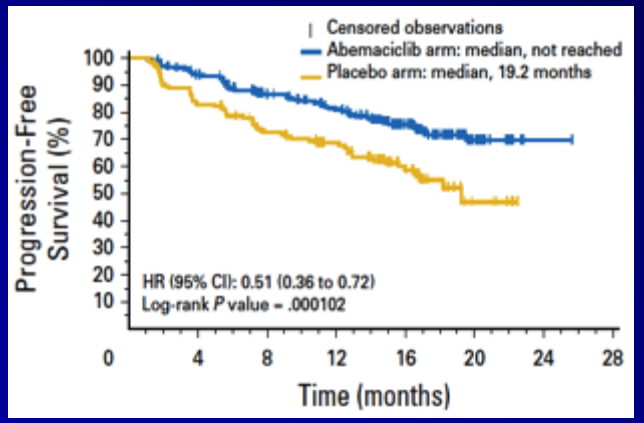
# CDK 4/6 Inhibitors: Details

| | Palbociclib (Ibrance, Pfizer) | Ribociclib (Kisqali, Novartis) | Abemiciclib (Verzenio, Lilly) |
|---|---|---|---|
| **Dose** | 125 mg daily | 600 mg daily | 200 mg twice daily |
| **Schedule** | 3 weeks on/ 1 week off | 3 weeks on/ 1 week off | Continuous |
| **Completed Phase III Trials** | 1st line: PALOMA-2<br>2nd line: PALOMA-3 | 1st line: MONALEESA-2, MONALEESA-7<br>2nd line: MONALEESA-3 | 1st line: MONARCH-3<br>1st or 2nd line: MONARCH-2<br>Single agent post chemo: MONARCH-1 |
| **FDA Approval Status** | 2015: 1st Line (letrozole)<br>2016: 2nd line (fulvestrant) | 2017: 1st line (letrozole)<br>2018: 1st and 2nd line (fulvestrant) pending | 2017: 2nd line (fulvestrant); Single agent post chemotherapy |

# CDKi + AIs: Progression-Free Survival 1st line




Palbociclib
PALOMA-2

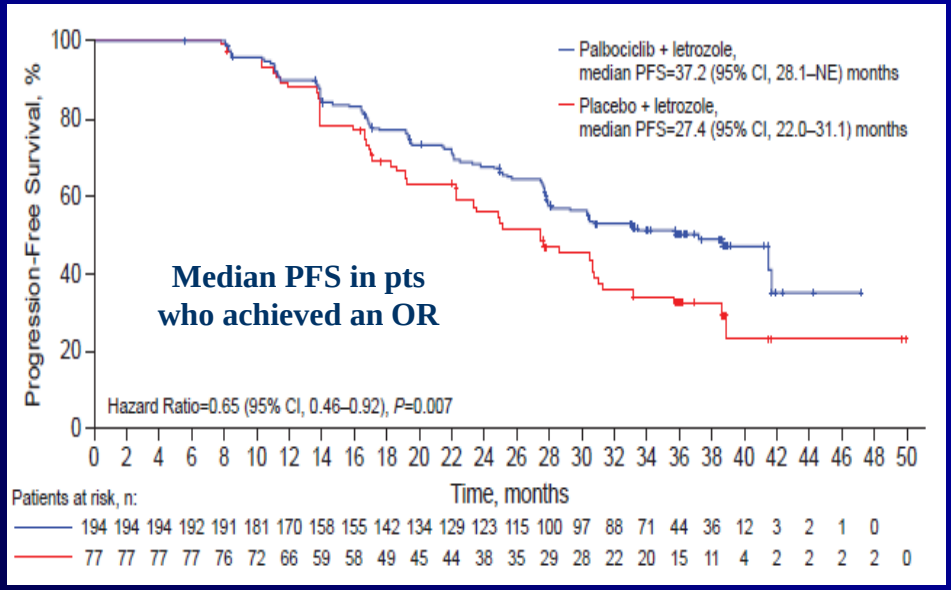
Ribociclib
MONALEESA-2

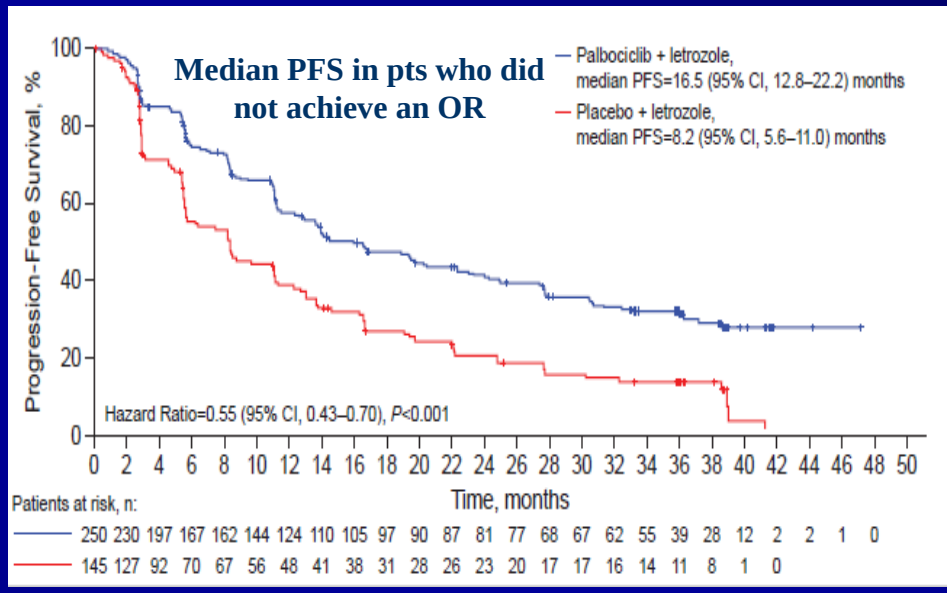
Abemiciclib
MONARCH-3

**Approximate doubling in PFS over endocrine therapy alone**

*Finn et al, NEJM, 2016 and Rugo et al, BCRT 2019 Hortobagyi et al, NEJM, 2016 and ASCO 2017; Goetz et al, JCO, 2017*

# PFS Outcome is Independent of Objective Response in Patients with HR+/HER2- ABC Treated with Palbociclib Plus Letrozole Compared to Letrozole: Analysis from PALOMA-2



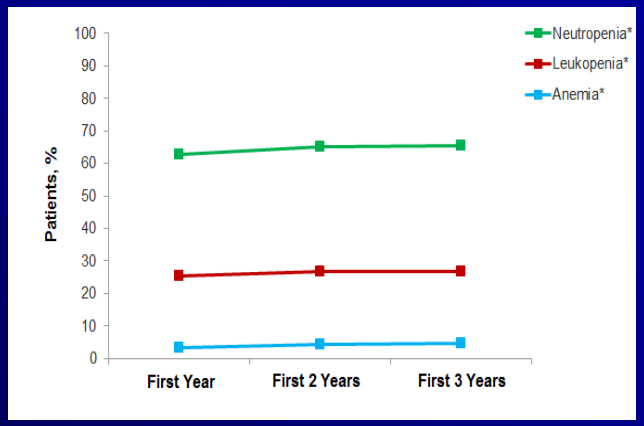

Rugo et al, ESMO 2018

# Phase III First-Line Studies in HR+ MBC

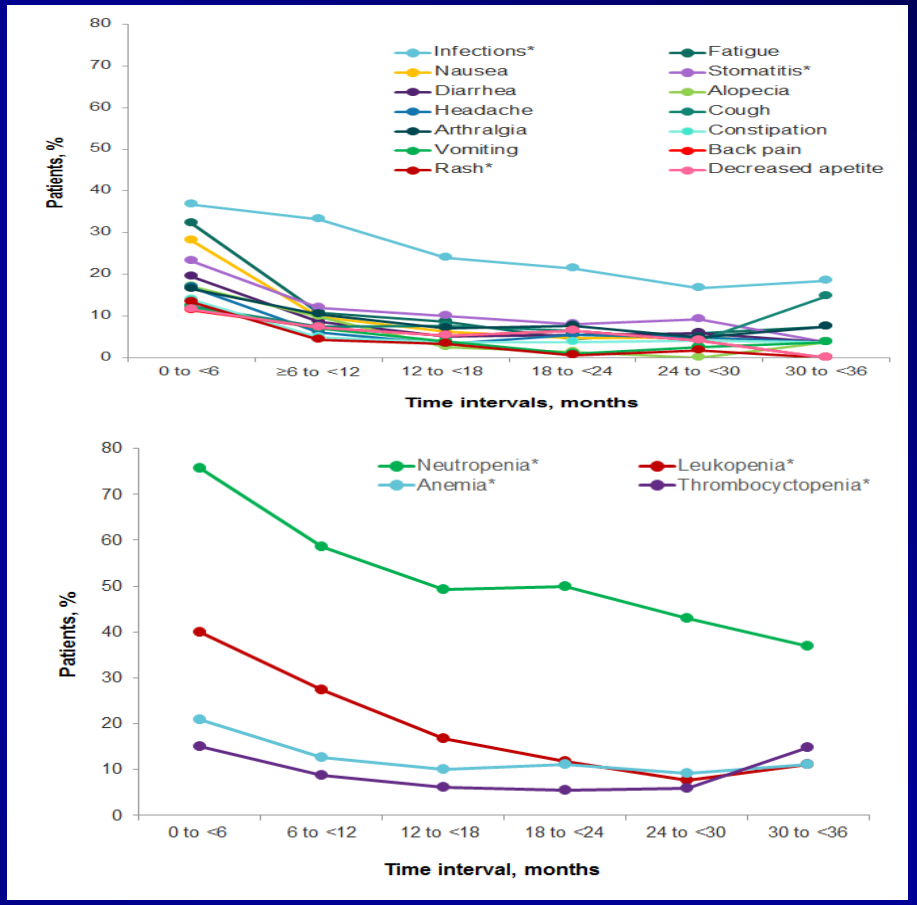
| | **Paloma-2**<br>**Finn et al, NEJM 2016; Rugo et al BCRT 2019** | **Monaleesa-2**<br>**Hortobagyi et al, NEJM 2016, ASCO 17** | **Monarch-3**<br>**Goetz et al, JCO 2017** | **Falcon**<br>**Robertson et al, Lancet 2016** |
|---|---|---|---|---|
| Study design | **Letrozole/Pla vs Let/Palbociclib (1:2)** | **Letrozole/Pla vs Let/Ribociclib (1:1)** | **Letrozole/Pla vs Let/Abemaciclib (1:2)** | **Anastrozole/Pla vs Fulvestrant/Pla** |
| No. of pts | 666<br>*No progression on AIs* | 668<br>*No progression on AIs* | *493*<br>*No progression on AIs* | 462<br>*No prior hormone therapy* |
| PFS | **14.5 vs 27.6 mo**<br>HR 0.56 (0.46-0.69)<br>p<0.000001 | **16.0 vs 25.3 mo**<br>HR 0.556 (0.43-0.72);<br>p=0.00000329 | **14.7 vs NR mo**<br>HR 0.53 (0.409-0.723)<br>P=0.000021 | **13.8 vs 16.6 mo.**<br>HR 0.797 (0.64- 0.999);<br>p=0.0486 |
| All oral | Yes | Yes | Yes | No |
| Subset difference | PFS benefit maintained with next therapy | NR | Yes but medians not yet reached | **13.8 v 22.3 mo in n= 218 (47%) without visceral disease**<br>No difference in those with visceral disease |

# Long-Term Safety: Paloma-2

Pooled incidence of hematologic toxicity, grade 3-4

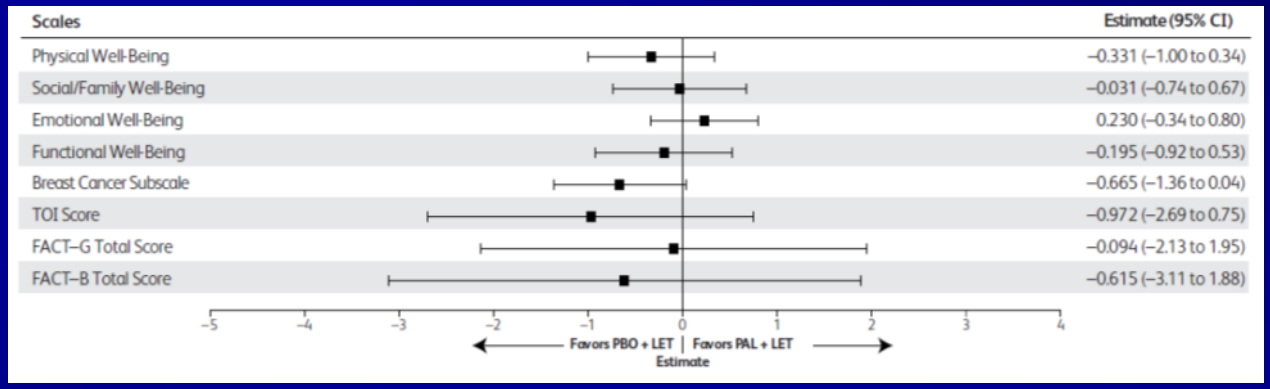


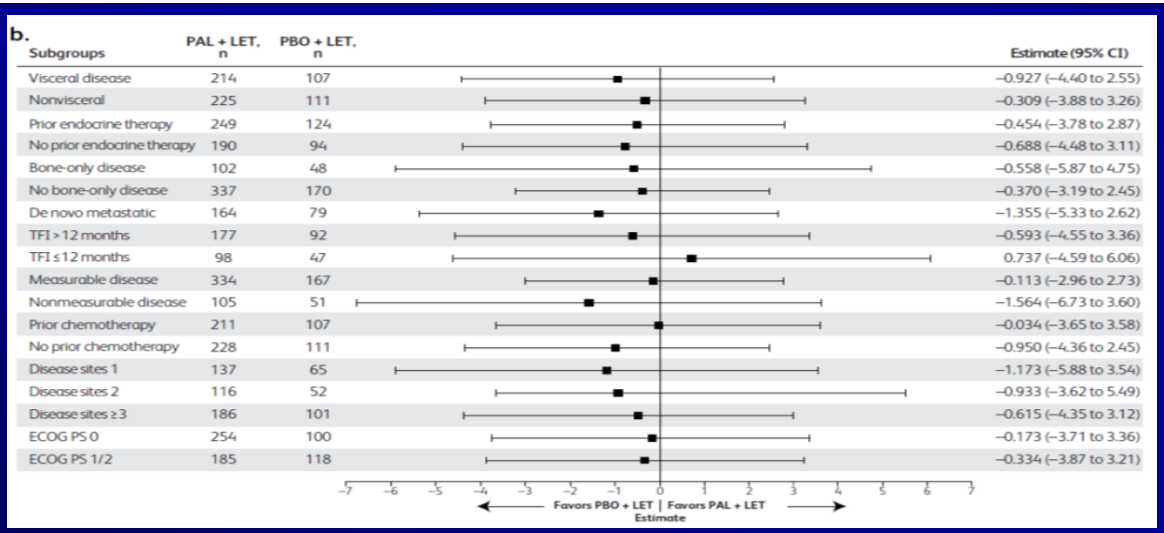

Pooled incidence of nonhematogic and hematologic adverse events by 6-month treatment intervals




Dieras et al, JNCI 2019

# Patient Reported Outcomes: FACT-B Scores in Paloma-2

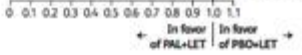


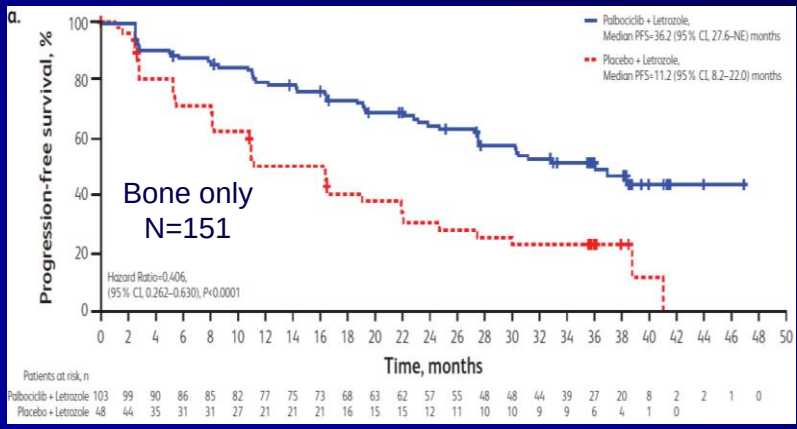



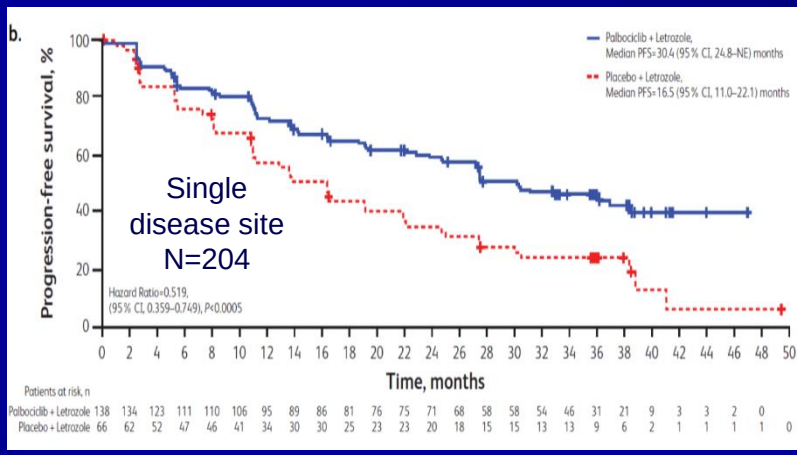

Rugo et al, BCRT 2019

# PALOMA-2 Subset Analysis

| Baseline Factors | PAL+LET Patients, n (%) | PBO+LET Patients, n (%) | PAL+LET mPFS (95% CI) | PBO+LET mPFS (95% CI) | PAL+LET vs PBO+LET HR (95% CI) | P* |
|---|---|---|---|---|---|---|
| All randomized patients, IA | 444 (100) | 222 (100) | 27.6 (22.4–30.3) | 14.5 (12.3–17.1) | 0.56 (0.46–0.69) | <0.0001 |
| All randomized patients, BICR | 444 (100) | 222 (100) | 35.7 (27.7–38.9) | 19.5 (16.6–26.6) | 0.61 (0.49–0.77) | <0.0001 |
| Visceral disease | 214 (48.2) | 110 (49.5) | 19.3 (16.4–24.2) | 12.3 (8.4–16.4) | 0.62 (0.47–0.81) | <0.0005 |
| Nonvisceral disease | 230 (51.8) | 112 (50.5) | 35.9 (27.7–NE) | 17.0 (13.8–24.8) | 0.50 (0.37–0.67) | <0.0001 |
| Bone-only disease | 103 (23.2) | 48 (21.6) | 36.2 (27.6–NE) | 11.2 (8.2–22.0) | 0.41 (0.26–0.63) | <0.0001 |
| No bone-only disease† | 341 (76.8) | 174 (78.4) | 24.2 (19.4–27.7) | 14.5 (12.9–18.5) | 0.62 (0.50–0.78) | <0.0001 |
| DFI† >12 mo | 179 (40.3) | 93 (41.9) | 30.3 (24.8–NE) | 13.8 (8.8–18.2) | 0.55 (0.40–0.76) | <0.0005 |
| DFI† ≤12 mo | 98 (22.1) | 48 (21.6) | 16.6 (13.9–24.2) | 11.0 (5.6–12.9) | 0.48 (0.32–0.72) | <0.0005 |
| DFI† >2 y | 154 (34.7) | 77 (34.7) | 38.5 (27.5–NE) | 16.6 (13.7–23.5) | 0.52 (0.36–0.75) | <0.0005 |
| DFI† >5 y | 90 (20.3) | 46 (20.7) | 38.6 (27.6–NE) | 23.5 (16.3–32.2) | 0.60 (0.36–1.00) | <0.05 |
| DFI† >10 y | 32 (7.2) | 23 (10.4) | NR (30.4–NE) | 23.5 (16.6–NE) | 0.44 (0.19–1.03) | <0.05 |
| De novo metastatic | 167 (37.6) | 81 (36.5) | 27.9 (22.1–33.4) | 22.0 (13.9–27.4) | 0.61 (0.44–0.85) | <0.005 |
| DFI from prior ET >12 mo | 156 (35.1) | 78 (35.1) | 27.6 (22.2–38.6) | 13.8 (8.2–16.6) | 0.58 (0.41–0.82) | <0.001 |
| DFI from prior ET ≤12 mo | 94 (21.2) | 48 (21.6) | 16.6 (13.9–24.2) | 11.0 (5.6–12.9) | 0.49 (0.33–0.73) | <0.0005 |
| Measurable disease | 338 (76.1) | 171 (77.0) | 23.7 (19.3–27.6) | 14.5 (12.3–18.5) | 0.63 (0.50–0.79) | <0.0001 |
| Nonmeasurable disease‡ | 106 (23.9) | 51 (23.0) | 36.2 (27.6–NE) | 16.5 (8.3–19.6) | 0.39 (0.25–0.60) | <0.0001 |
| No prior ET with visceral disease | 86 (19.4) | 47 (21.2) | 23.7 (16.8–30.3) | 13.9 (10.2–22.2) | 0.55 (0.36–0.85) | <0.005 |
| No prior ET without visceral disease | 108 (24.3) | 49 (22.1) | 36.2 (27.9–NE) | 27.6 (19.1–35.6) | 0.59 (0.38–0.92) | <0.01 |
| Prior ET | 250 (56.3) | 126 (56.8) | 24.2 (18.8–27.6) | 11.2 (8.4–14.5) | 0.54 (0.42–0.71) | <0.0001 |
| No prior ET | 194 (43.7) | 96 (43.2) | 30.3 (24.5–35.7) | 21.9 (15.9–27.4) | 0.59 (0.43–0.80) | <0.0005 |
| Prior chemotherapy | 213 (48.0) | 109 (49.1) | 24.8 (19.3–27.9) | 12.9 (9.6–16.5) | 0.53 (0.40–0.71) | <0.0001 |
| No prior chemotherapy | 231 (52.0) | 113 (50.9) | 27.9 (23.2–33.4) | 18.5 (13.6–24.8) | 0.59 (0.45–0.79) | <0.0005 |
| Disease site, 1 | 138 (31.1) | 66 (29.7) | 30.4 (24.8–NE) | 16.5 (11.0–22.1) | 0.52 (0.36–0.75) | <0.0005 |
| Disease sites, 2 | 117 (26.4) | 52 (23.4) | 28.1 (19.4–NE) | 16.3 (11.0–27.4) | 0.57 (0.37–0.89) | <0.01 |
| Disease sites, ≥3 | 189 (42.6) | 104 (46.8) | 23.7 (19.2–27.6) | 13.8 (8.8–17.0) | 0.61 (0.46–0.82) | <0.0005 |
| ECOG PS 0 | 257 (57.9) | 102 (45.9) | 27.9 (24.9–36.2) | 19.3 (14.5–24.9) | 0.65 (0.48–0.87) | <0.005 |
| ECOG PS 1/2 | 187 (42.1) | 120 (54.1) | 22.2 (16.6–27.7) | 11.8 (8.3–16.5) | 0.51 (0.39–0.68) | <0.0001 |
| Age <65 y | 263 (59.2) | 141 (63.5) | 23.2 (19.3–27.6) | 13.7 (11.0–16.6) | 0.55 (0.43–0.70) | <0.0001 |
| Age ≥65 y | 181 (40.8) | 81 (36.5) | 30.6 (27.6–NE) | 19.1 (11.0–30.4) | 0.60 (0.43–0.86) | <0.005 |

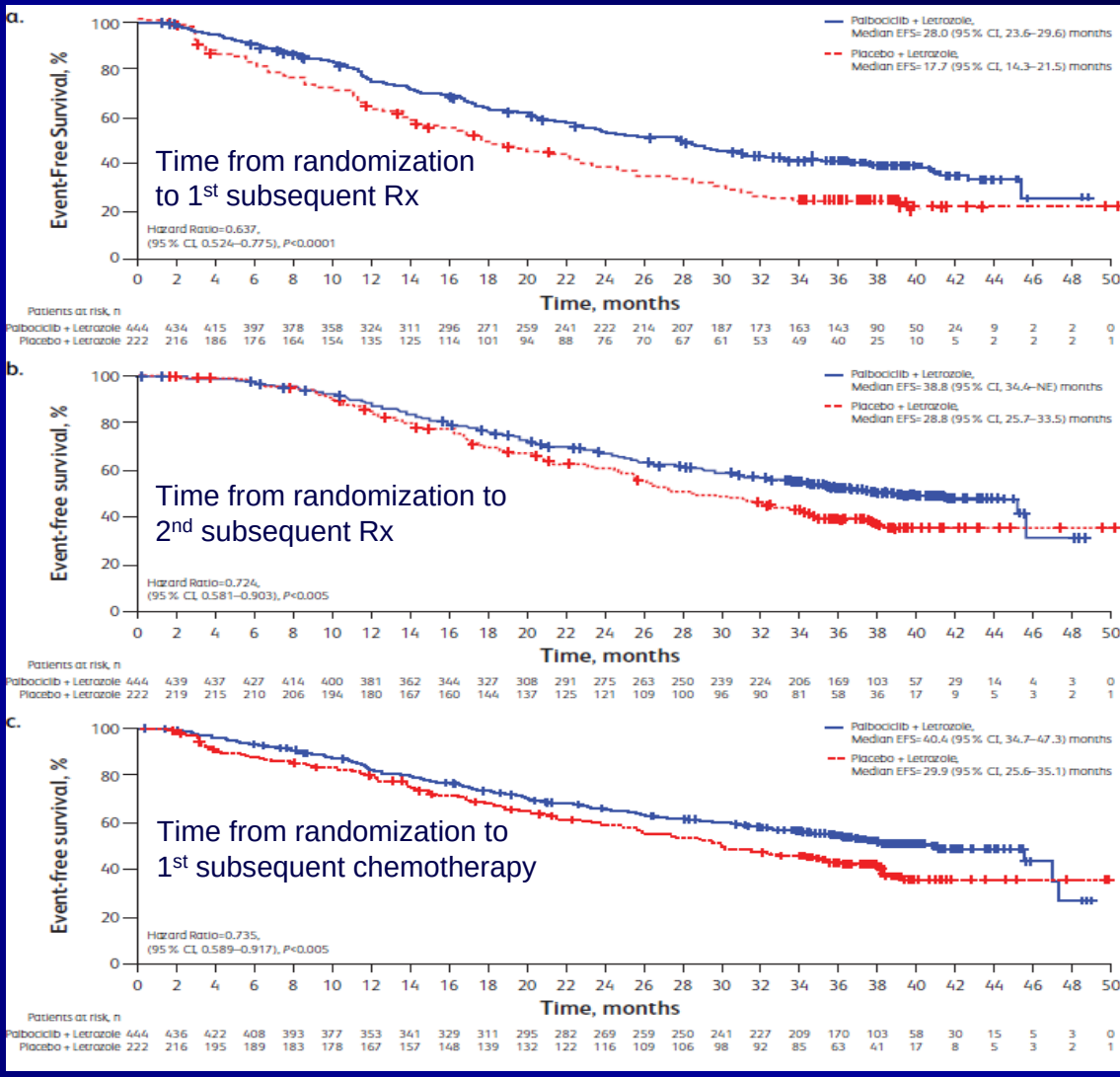



Rugo et al, BCRT 2019

# Time to Initiation of Subsequent Anti-Cancer Therapies




Rugo et al, BCRT 2019

# Fulvestrant with CDK4/6i as First Line Therapy for HR+ MBC: MONALEESA 3

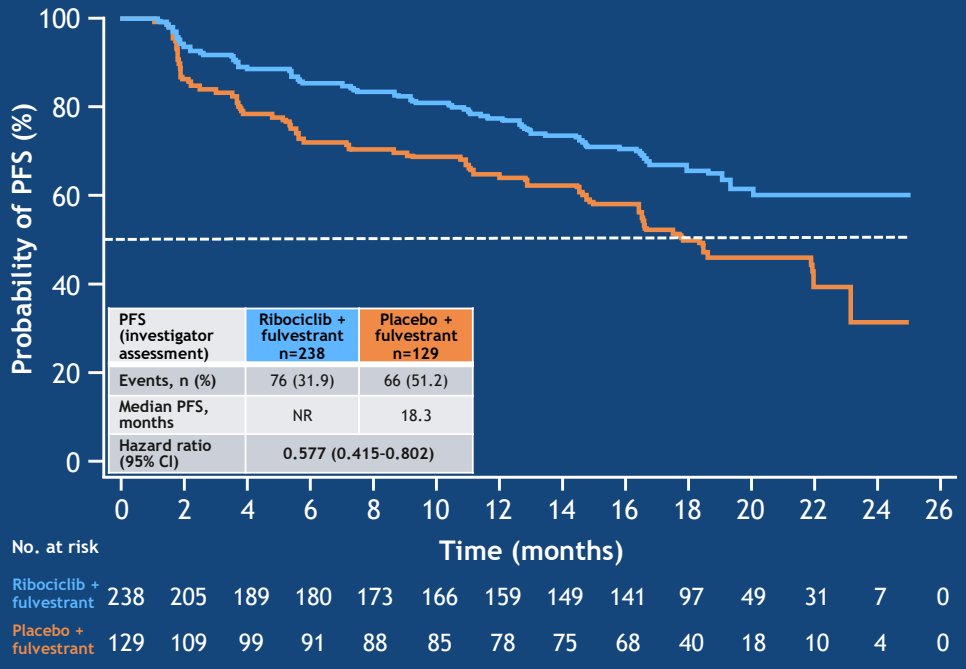
- Randomized phase III placebo controlled trial of ribociclib and fulvestrant
  - 2:1 randomization, n=726
  - No prior chemothrapy, measurable disease
  - No or <1 line of prior endocrine therapy for MBC

| | | |
|---|---|---|
| **Prior endocrine therapy status‖** | | |
| First line¶ | 238 (49.2) | 129 (53.3) |
| Second line + early relapsers** | 236 (48.8) | 109 (45.0) |
| **Prior endocrine therapy setting** | | |
| (Neo)adjuvant | 289 (59.7) | 142 (58.7) |
| Advanced | 110 (22.7) | 40 (16.5) |

Slamon et al, JCO 2018

# PFS by prior endocrine therapy status

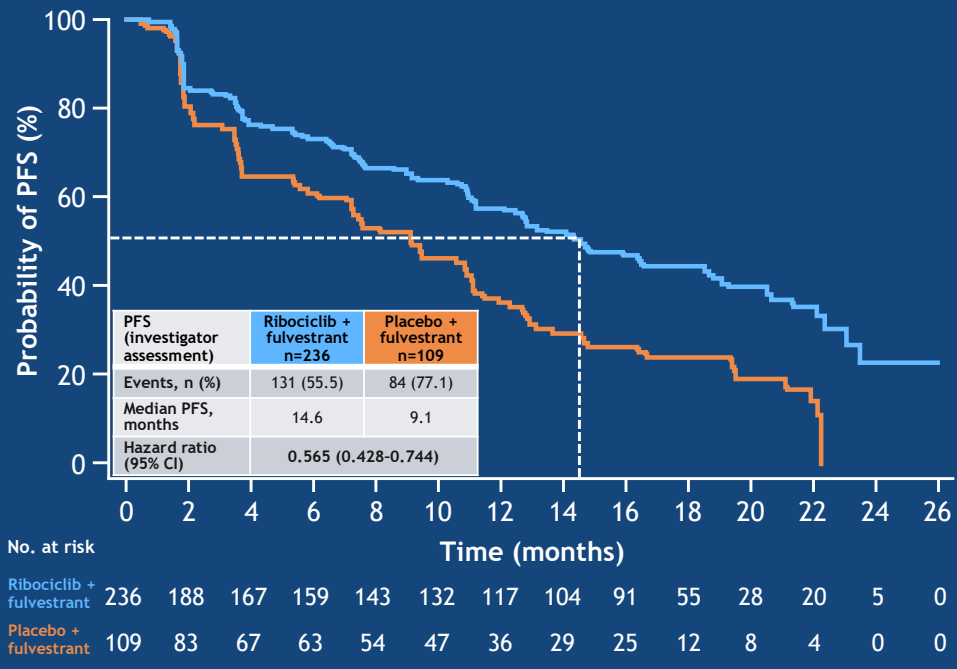
## First line*




| PFS (investigator assessment) | Ribociclib + fulvestrant n=238 | Placebo + fulvestrant n=129 |
|---|---|---|
| Events, n (%) | 76 (31.9) | 66 (51.2) |
| Median PFS, months | NR | 18.3 |
| Hazard ratio (95% CI) | 0.577 (0.415-0.802) | |

| No. at risk | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ribociclib + fulvestrant | 238 | 205 | 189 | 180 | 173 | 166 | 159 | 149 | 141 | 97 | 49 | 31 | 7 | 0 |
| Placebo + fulvestrant | 129 | 109 | 99 | 91 | 88 | 85 | 78 | 75 | 68 | 40 | 18 | 10 | 4 | 0 |

## Second line + early relapsers‡



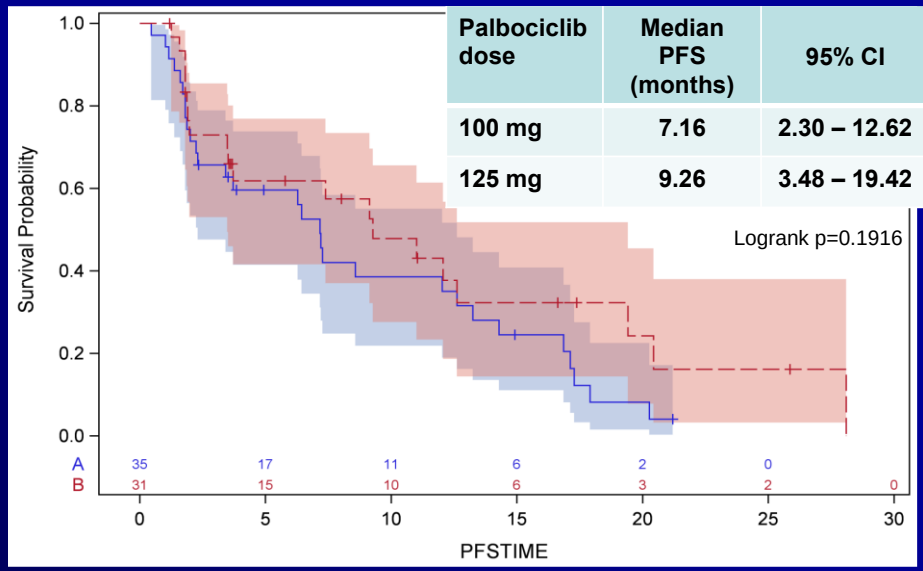

| PFS (investigator assessment) | Ribociclib + fulvestrant n=236 | Placebo + fulvestrant n=109 |
|---|---|---|
| Events, n (%) | 131 (55.5) | 84 (77.1) |
| Median PFS, months | 14.6 | 9.1 |
| Hazard ratio (95% CI) | 0.565 (0.428-0.744) | |

| No. at risk | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ribociclib + fulvestrant | 236 | 188 | 167 | 159 | 143 | 132 | 117 | 104 | 91 | 55 | 28 | 20 | 5 | 0 |
| Placebo + fulvestrant | 109 | 83 | 67 | 63 | 54 | 47 | 36 | 29 | 25 | 12 | 8 | 4 | 0 | 0 |

*Treatment naive for ABC; ‡Received up to 1 line of prior endocrine therapy for ABC.

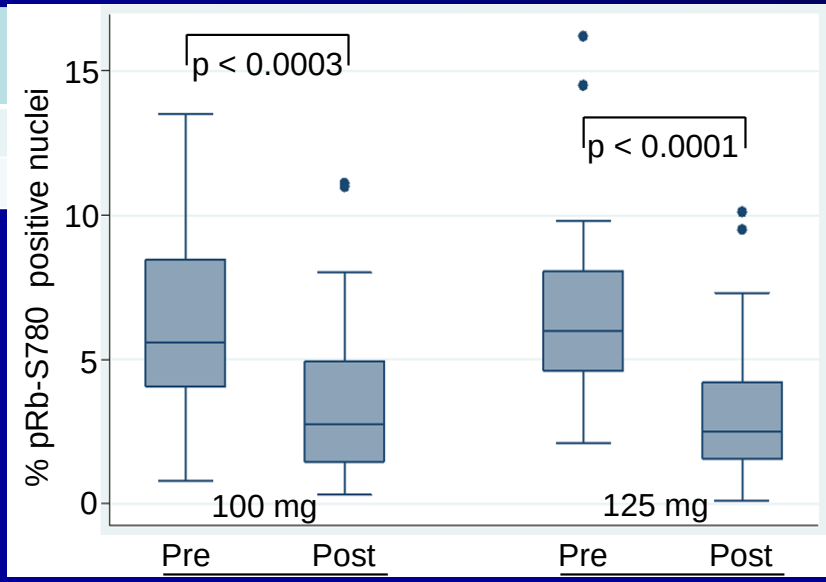
| Toxicity in 1st line | Palbociclib | Ribociclib | Abemaciclib |
|---|---|---|---|
| Dosing schedule | 3 wks on, one wk off | 3 wks on, one wk off | Continuous |
| ≥Gr 3 neutropenia | 66% | 59.6% | 21.1% |
| Febrile neutropenia | 1.6% | 1.5% | <1% |
| ≥Gr 3 diarrhea (all grade) | 1% (26%) | 1.2% (35%) | 9.5 (81%) |
| Gr2/3 QTc prolongation | - | 3/0.3 | - |
| ≥Gr 3 AST/ALT increase | - | 5.7/9.3% | 3.8/7% |
| Dose reduction/discontin due to AEs | 36% / 9.7% | 51% / 7.4% | 43.4% / 19.6% |
| Alopecia | 33% | 33% | 27% |
| Increased creatinine | - | - | 98% (nl fcn) |
| VTE/PE | 0.9 vs 1.4% | NR | 4.9 vs 0.6% |

# Palbociclib with Fulvestrant or Tamoxifen for HR+ MBC with Prior Chemotherapy for Advanced Disease (TBCRC 035): A Phase II Study with Pharmacodynamic Markers




| Palbociclib dose | Median PFS (months) | 95% CI | Range (months) |
|---|---|---|---|
| 100 mg | 7.16 | 2.30 – 12.62 | 0.46-21.19 |
| 125 mg | 9.26 | 3.48 – 19.42 | 1.18-28.09 |

100 vs 125 mg by total number of grade 3/4 neutropenia events per patient:
Two sided Wilcoxon Rank-Sum p-value = 0.036




% of nuclei with pRb (S780) and Ki67-positive nuclei significantly lower in post-Rx skin biopsies

No significant difference between % change in pRb and Ki67 in post-Rx biopsies and dose of palbociclib (p>0.1)

No impact of lower dose on response, PFS, inhibition of pRB or Ki67

Rugo et al, AACR 2019

# CDKi in Endocrine Pre-Treated

| | PALOMA 3 | MONARCH 2 | MONALEESA 3 |
|---|---|---|---|
| Treatment | Fulvestrant/palbociclib vs fulvestrant/PLA | Fulvestrant/abemaciclib vs fulvestrant/PLA | Fulvestrant/ribociclib vs fulvestrant/PLA |
| Number | 521 | 699 | 345 (2nd line) |
| Randomization | 2:1 | 2:1 | 2:1 |
| **Prior chemotherapy for met disease (%)** | **31-36%** | **0** | **0** |
| ET resistance (%)<br>Primary<br>Secondary | <br>20<br>79 | <br>25<br>73 | <br>NR |
| Prior AI | 85-87% | 67-71% | 59=60% |

Primary ET Resistance:

- Progression on the 1st 2 years of adjuvant ET, OR on the 1st 6 months of 1st line ET for MBC

Secondary ET Resistance:

- Progression after 2 years on adjuvant ET, within 12 months of end of adjuvant ET, OR after 6 months on ET for MBC

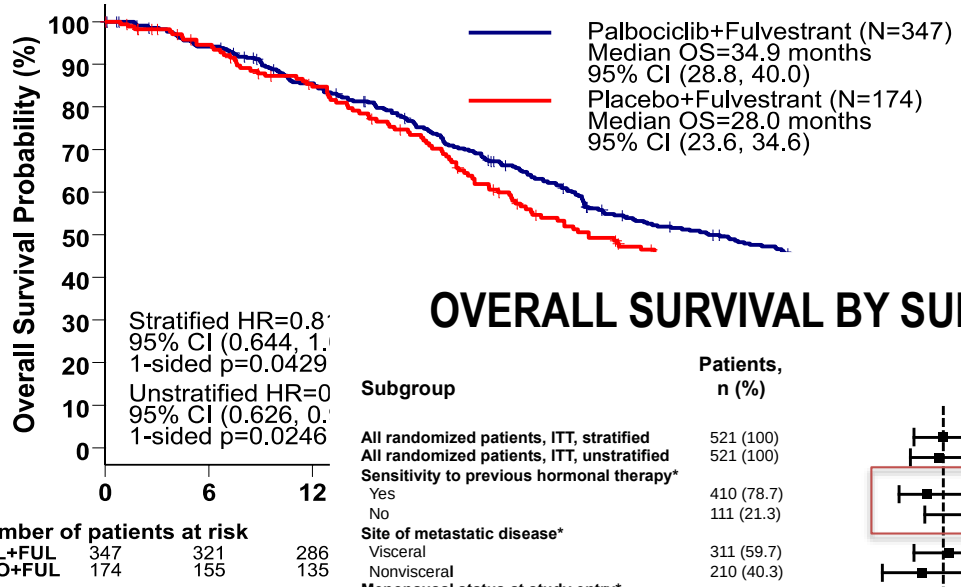
Cardoso F et al. *The Breast* 6:489-502, 2014;; Cardoso F et al. *Ann Oncol* 25:1871-88, 2014.

# Comparison of Trials in Patients with Progression on Prior NSAI

| | PALOMA 3<br>Turner et al, NEJM 2015, NEJM 2018 | MONARCH 2<br>Sledge et al, JCO 2017 | MONALEESA 3<br>Slamon et al, JCO 2018 | BOLERO 2<br>Baselga et al, NEJM 2012, Yardley et al, Adv Ther 2013 | PreCOG<br>Kornblum et al, SABCS 2016 |
|---|---|---|---|---|---|
| **Study design** | Fulvestrant/pla vs fulvestrant/ palbociclib | Fulvestrant/pla vs fulvestrant/ abemaciclib | Fulvestrant/pla vs fulvestrant/ ribociclib | Exemestane/pla vs exemestane/EVE | Fulvestrant/pla vs fulvestrant/EVE |
| **Patient #** | 521 | 699 | 345 (2nd line) | 724 | 131 |
| **PFS (mo) p value (HR)** | 4.6 vs 11.2<br>(p<.0001<br>(HR 0.5) | 9.3 vs 16.4<br>P<.0000001<br>(HR 0.55) | 9.1 vs 14.6<br>(HR 0.565) | 3.2 vs 7.8 (inv)<br>4.1 vs 11 (central)<br>p<.0001<br>(HR 0.38) | 5.1 vs 10.4<br>p=.02<br>(HR 0.6)<br>12 mo PFS in MANTA trial! (Schmid et al, SABCS 2017) |

No differences in subset analysis

# OVERALL SURVIVAL (ITT)

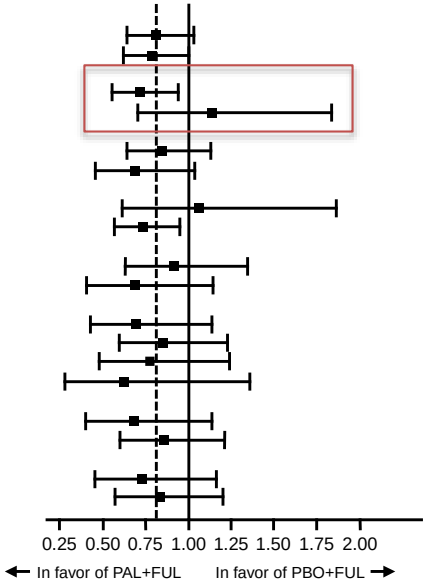



- **Absolute improvement in media**

The prespecified significa
adjusted

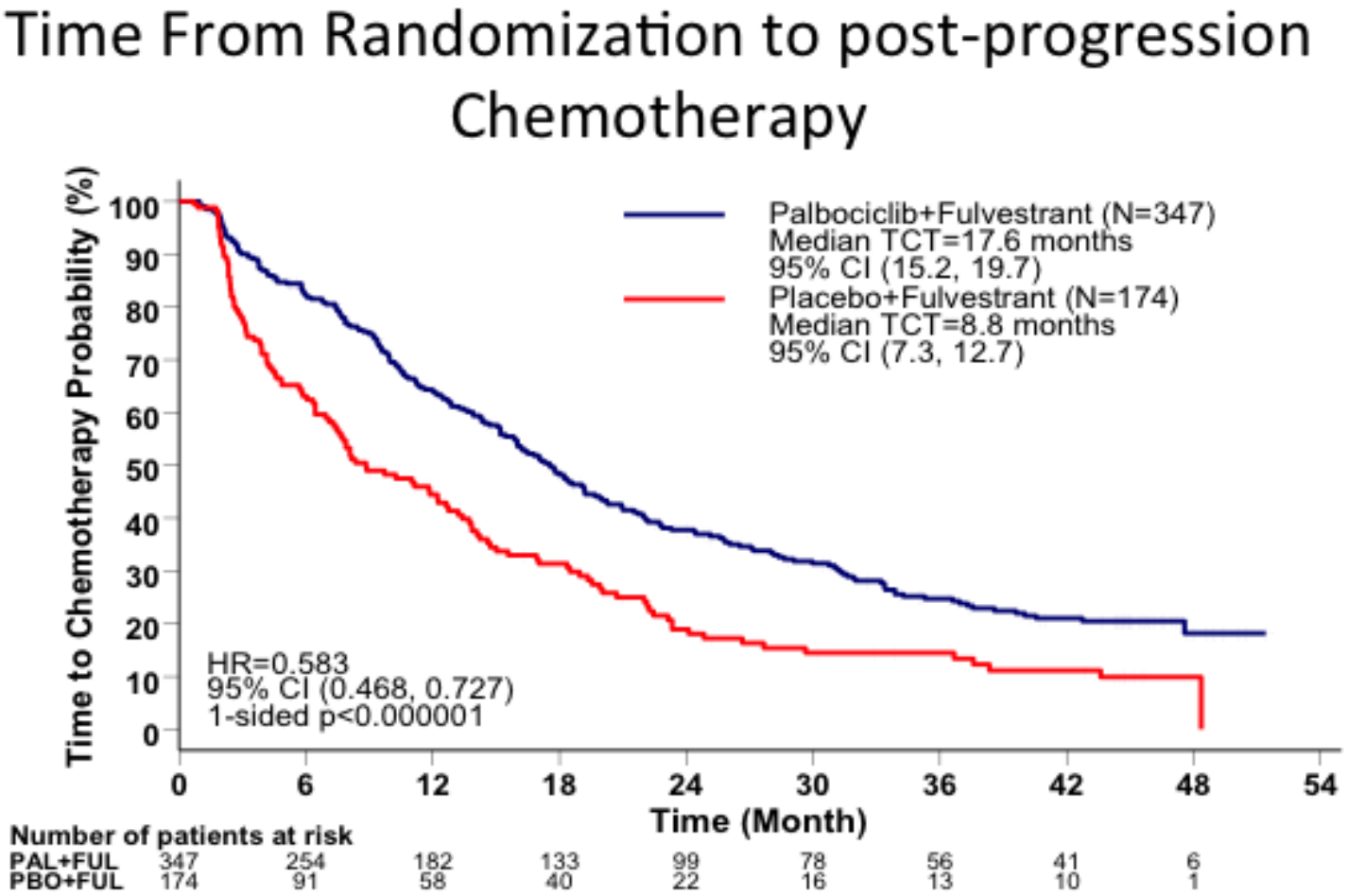
## OVERALL SURVIVAL BY SUBGROUPS

| Subgroup | Patients, n (%) | HR (95% CI) | PAL+FUL Median OS (95% CI) | PBO+FUL Median OS (95% CI) | Interaction *P* Value |
|---|---|---|---|---|---|
| **All randomized patients, ITT, stratified** | 521 (100) | 0.81 (0.64–1.03) | 34.9 (28.8–40.0) | 28.0 (23.6–34.6) | |
| **All randomized patients, ITT, unstratified** | 521 (100) | 0.79 (0.63–1.00) | 34.9 (28.8–40.0) | 28.0 (23.6–34.6) | |
| **Sensitivity to previous hormonal therapy*** | | | | | 0.12 |
| Yes | 410 (78.7) | 0.72 (0.55–0.94) | 39.7 (34.8–45.7) | 29.7 (23.8–37.9) | |
| No | 111 (21.3) | 1.14 (0.71–1.84) | 20.2 (17.2–26.4) | 26.2 (17.5–31.8) | |
| **Site of metastatic disease*** | | | | | 0.44 |
| Visceral | 311 (59.7) | 0.85 (0.64–1.13) | 27.6 (24.4–31.2) | 24.7 (20.8–31.8) | |
| Nonvisceral | 210 (40.3) | 0.69 (0.46–1.04) | 46.9 (39.3–NE) | 35.4 (24.6–NE) | |
| **Menopausal status at study entry*** | | | | | 0.25 |
| Pre/peri | 108 (20.7) | 1.07 (0.61–1.86) | 38.0 (24.4–NE) | 38.0 (22.2–NE) | |
| Post | 413 (79.3) | 0.73 (0.57–0.95) | 34.8 (28.8–40.1) | 27.1 (22.8–32.1) | |
| **Prior chemotherapy** | | | | | 0.66 |
| Metastatic treatment | 177 (34.0) | 0.91 (0.63–1.32) | 25.6 (21.4–30.1) | 26.2 (20.0–37.5) | |
| None | 130 (25.0) | 0.68 (0.41–1.15) | 46.2 (36.5–NE) | 29.7 (22.8–NE) | |
| **Prior lines of therapy in metastatic setting** | | | | | 0.88 |
| 0 | 114 (21.9) | 0.70 (0.43–1.14) | 36.1 (27.6–43.7) | 24.7 (19.5–34.6) | |
| 1 | 225 (43.2) | 0.86 (0.60–1.22) | 38.0 (27.7–46.5) | 33.8 (23.5–41.4) | |
| 2 | 131 (25.1) | 0.76 (0.48–1.22) | 30.0 (23.0–40.1) | 24.3 (20.0–29.7) | |
| ≥3 | 51 (9.8) | 0.64 (0.29–1.40) | 34.8 (26.1–NE) | 27.1 (5.3–NE) | |
| **ESR1 mutation status†** | | | | | 0.60 |
| Positive | 106 (20.3) | 0.69 (0.43–1.12) | 35.6 (23.6–42.0) | 24.6 (19.7–33.0) | |
| Negative | 289 (55.5) | 0.85 (0.61–1.19) | 36.5 (28.0–43.1) | 31.8 (22.8–39.1) | |
| **PIK3CA mutation status†** | | | | | 0.64 |
| Positive | 133 (25.5) | 0.74 (0.48–1.14) | 28.6 (25.3–39.3) | 22.2 (15.7–29.5) | |
| Negative | 262 (50.3) | 0.84 (0.59–1.18) | 38.8 (28.9–44.5) | 33.0 (24.3–41.6) | |




Turner et al, NEJM 2018; Cristofanilli, ESMO 2018

Rx

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**In patients with sensitivity to prior ET, absolute improvement in median OS in the palbociclib arm vs the placebo arm was 10.0 months.**

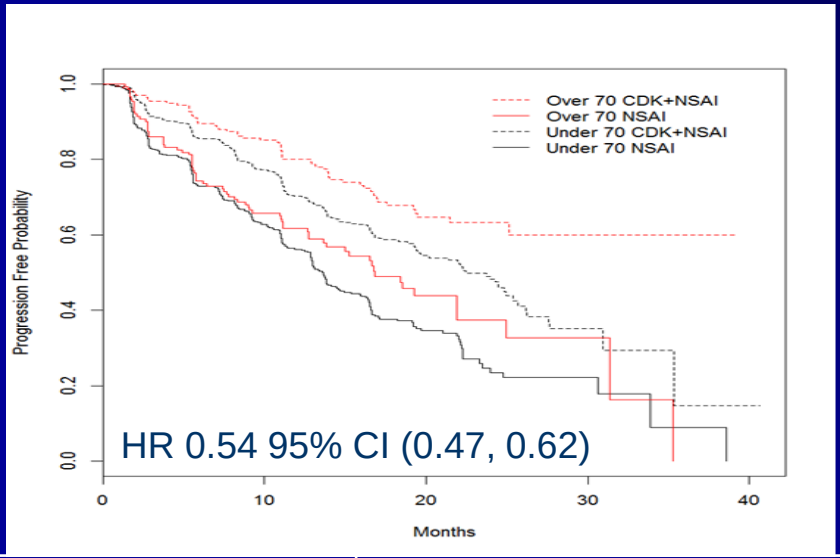
# Premenopausal Women: Phase III Data

- PALOMA-3 subset analysis (Loibl et al, Oncologist 2017)
  - N=108; fulvestrant plus OFS
  - Similar efficacy and toxicity
- MONALEESA-7 (Tripathy et al, Lancet Oncol 2018)
  - N=672, randomized 1:1 to tamoxifen/NSAI plus goserelin +/- ribociclib or placebo
    - 26% received tamoxifen, 74% NSAIs
  - Efficacy similar to MONALEESA-2
  - PFS: 13 vs 23.8 months; HR 0.55 (0.44-0.69), p 0.0000000983
    - HR: similar between tamoxifen and NSAI
    - No difference in toxicity
  - Updated data expected ASCO 2019
- Exemestane/OS plus palbociclib (Young Pearl trial at ASCO 2019*)
- Important: Overall approach for pre-menopausal women on ovarian suppression should mimic that for post-menopausal women (Rugo et al, ASCO guidelines 2017)

*Yeon-Hee Park presenting

# US FDA Pooled Retrospective Subset Analysis of CDKi in Older Women

- Enrolled on registration trials submitted to the FDA
  - First-line therapy with AI plus CDK 4/6i
  - 329 of 1992 total patients aged ≥70
- Patient characteristics
  - 52% de novo metastatic disease, 38% adjuvant hormone therapy
- No rx differences across age subgroups regardless of age cut off




| | Median PFS (95% CI) |
|---|---|
| Age≥70 CDK4/6 (n=280) | NR (25.1 months, NR) |
| Age <70 CDK4/6 (n=826) | 23.75 months (21.9, 25.4) |
| Age ≥70 AI only | 16.8 months (13.7, 21.9) |
| Age <70 AI only | 13.8 months (12.9, 14.7) |

Singh et al, SABCS 2017

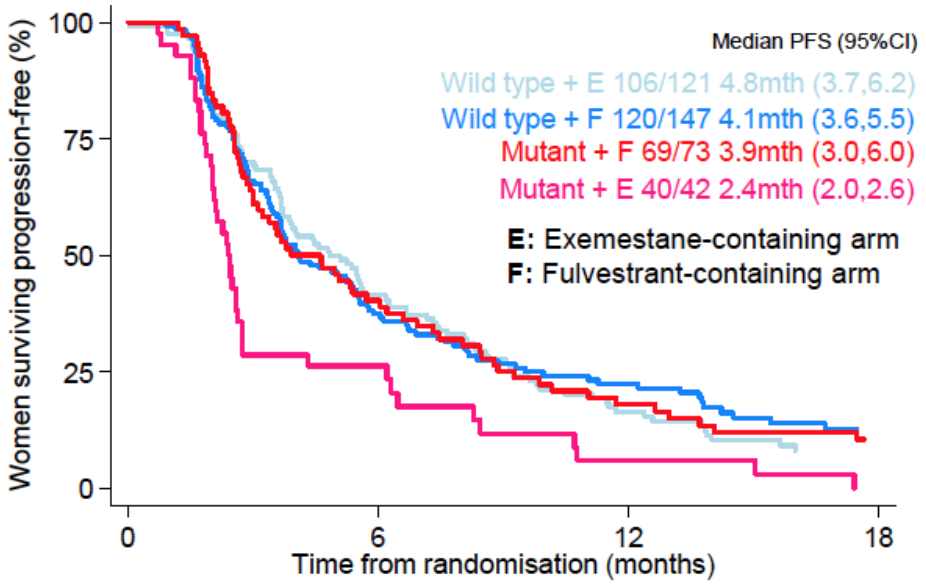
# Tolerability and Safety

| | Age < 65 years N = 625 (%) | Age ≥ 65 years N = 479(%) | Age ≥ 70 years N = 280 (%) |
|---|---|---|---|
| Grade 1-2 Adverse Events | 610 (98) | 470 (98) | 277 (99) |
| Grade 3-4 Adverse Events | 417 (66) | 385 (80) | 229 (82) |
| Grade 5 Adverse Events | 7 (1) | 11 (2) | 8 (3) |

| | Age < 65 years N = 625 (%) | Age ≥ 65 years N = 479 (%) | Age ≥ 70 years N = 280 (%) |
|---|---|---|---|
| AE leading to dose reduction and/or interruption | 411 (66) | 360 (75) | 216 (77) |
| AE leading to discontinuation | 50 (8) | 76 (16) | 48 (17) |
| Serious Adverse Events | 103 (16) | 147 (31) | 93 (33) |

# Can we Identify Which Tumors are More Sensitive to Specific Hormone Therapy with NGS?

# SoFEA and EFECT meta-analysis for baseline detection of *ESR1* mutations




| N at risk (events) | | | | | | | |
|---|---|---|---|---|---|---|---|
| Wild type + E | 121 | (70) | 49 | (28) | 17 | (8) | 7 |
| Wild type + F | 147 | (87) | 50 | (19) | 25 | (10) | 8 |
| Mutant + E | 42 | (31) | 9 | (7) | 2 | (2) | 0 |
| Mutant + F | 73 | (43) | 29 | (16) | 12 | (5) | 6 |

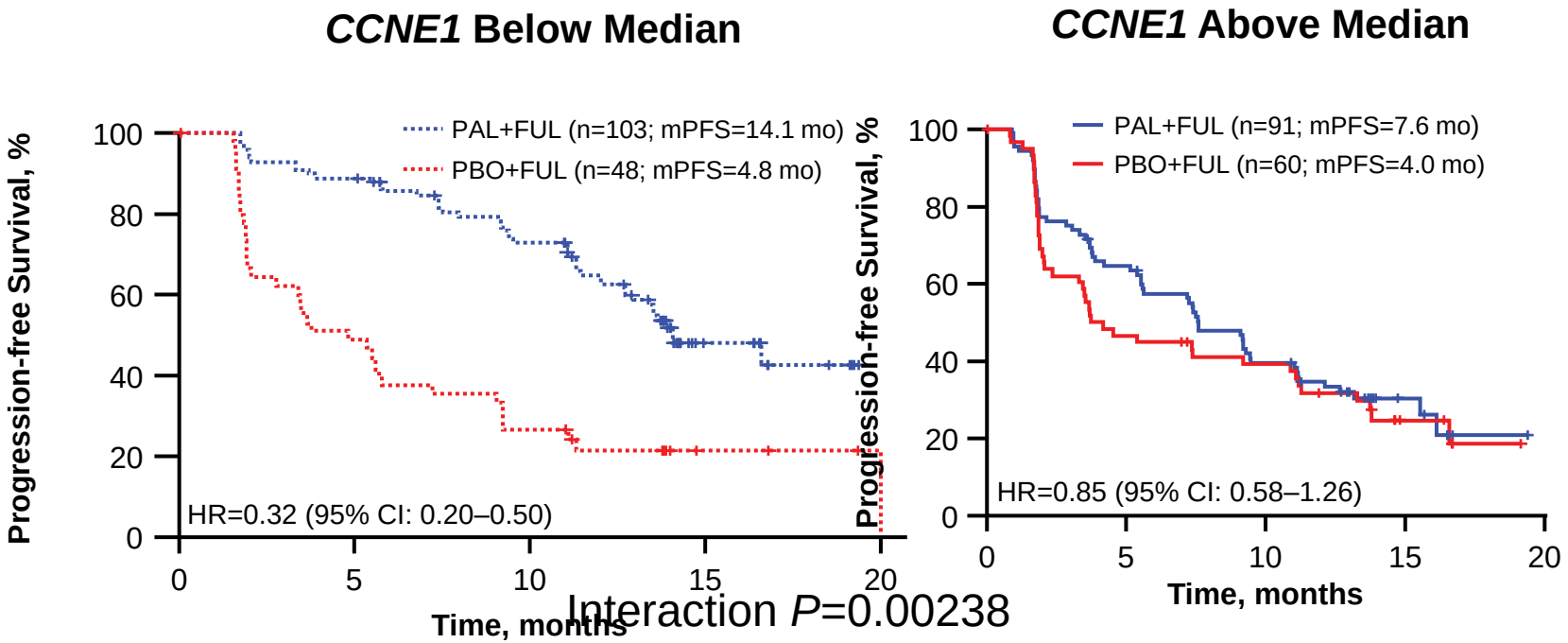
PFS improved on fulvestrant compared to exemestane for those with ESR1 mutations P=.01, HR 0.59; no difference for wild type

# Mechanisms of Resistance to CDK 4/6i

- de novo resistance may be rare and hard to detect
  - High clinical benefit observed in phase III trials
  - Loss of RB results in mechanistic resistance
- Resistance acquired in patients progressing on CDK 4/6i
  - RB alterations: mutations acquired on fulvestrant/palbo in ~5%[1]
  - Amplification of S phase CDKs, cyclins, ?amp of cyclin D1
    - Bypass CDK 4/6 by activating CDK2 through overexpression/amplification of CCNE 1/2[2]
  - Upregulation of signalling pathways that induce cyclins/ CDKs
    - PI3K, FGFR, RAS
  - Acquired ESR1 mutations result in resistance to hormone therapy

O'Leary et al, Cancer Discovery 2018, Turner et al, JCO 2019

# Higher Expression of *CCNE1 is* Associated with Relative Resistance to Palbociclib



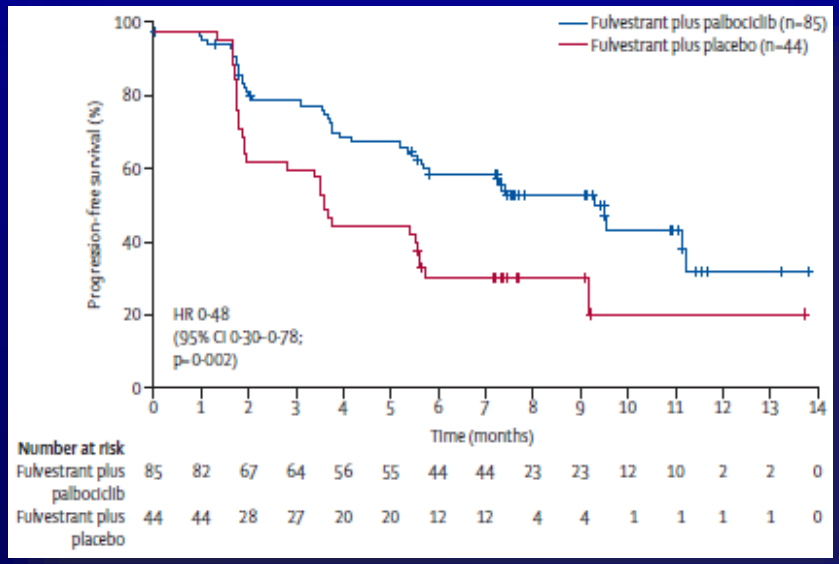

- High levels of rb-E2F gene expression signatures were associated with relative resistance to palbociclib
-

Data cutoff: Oct 23, 2015

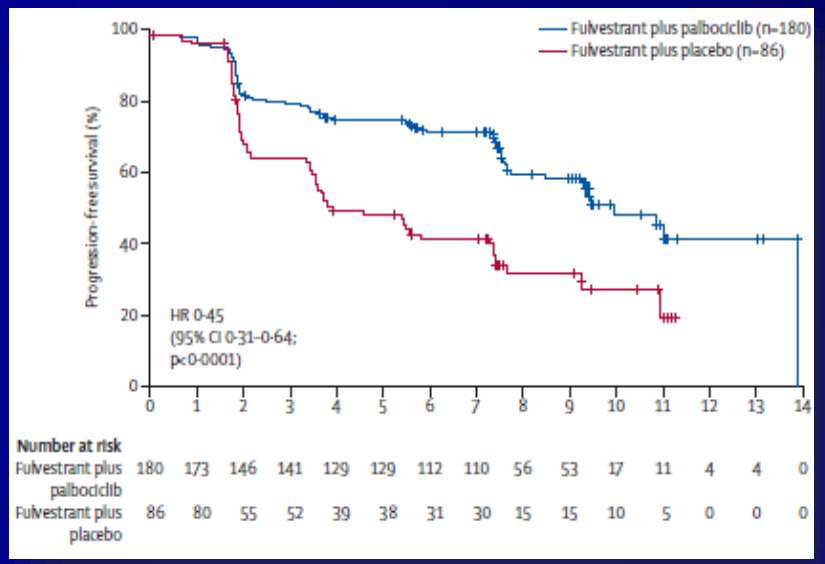
***Turner N et al JCO 2019***

# *PIK3CA* mutation status & response to CDK4/6 inhibitors in PALOMA-3

## *PIK3CA* mutant




## *PIK3CA* WT

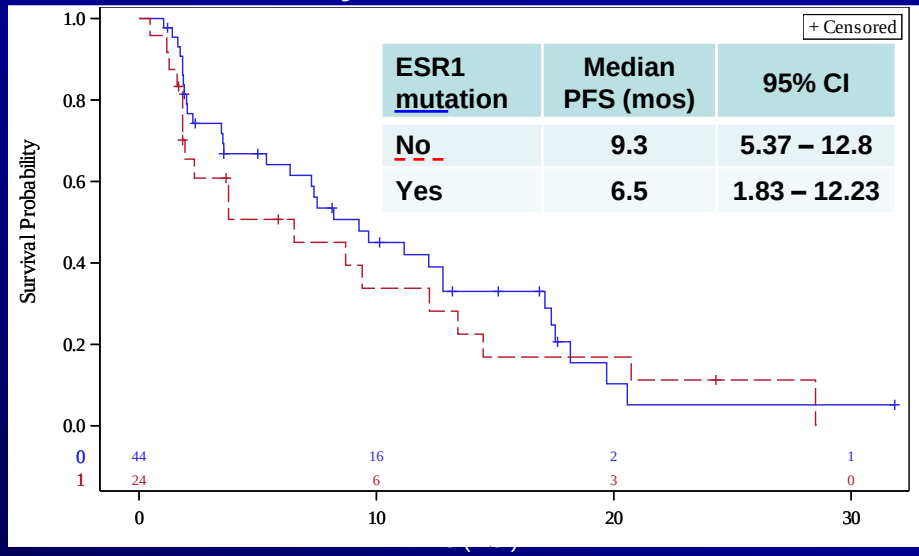



**In Paloma 3, PIK3CA mutations did not predict response to CDK4 inhibitors**

*Cristofanilli M, et al. Lancet Oncol. 2016;17(4):425–439.*

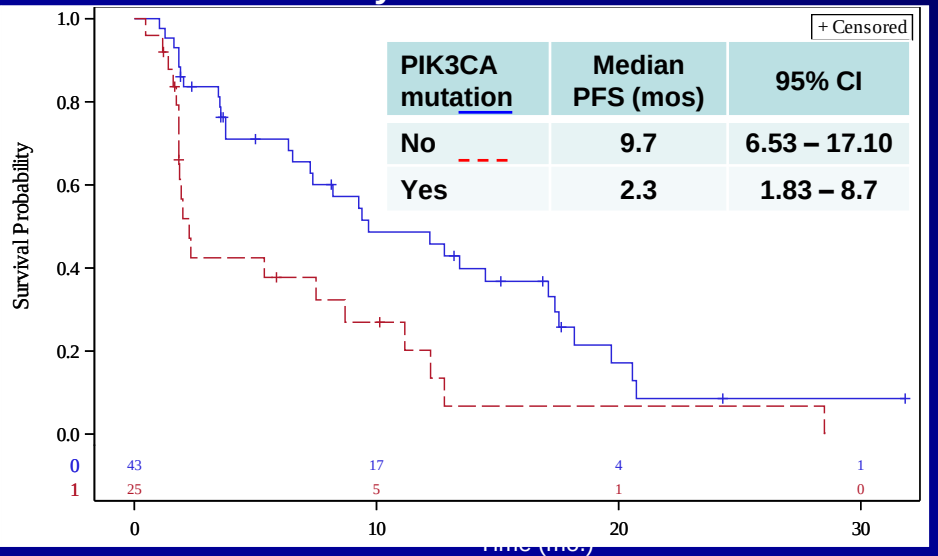
# TBCRC 035: PFS based on PIK3CA and ESR1 by cfDNA

**PFS by ESR1 Mutation Status**




| ESR1 mutation | Median PFS (mos) | 95% CI |
|---|---|---|
| No | 9.3 | 5.37 – 12.8 |
| Yes | 6.5 | 1.83 – 12.23 |

**PFS by PIK3CA Mutation Status**

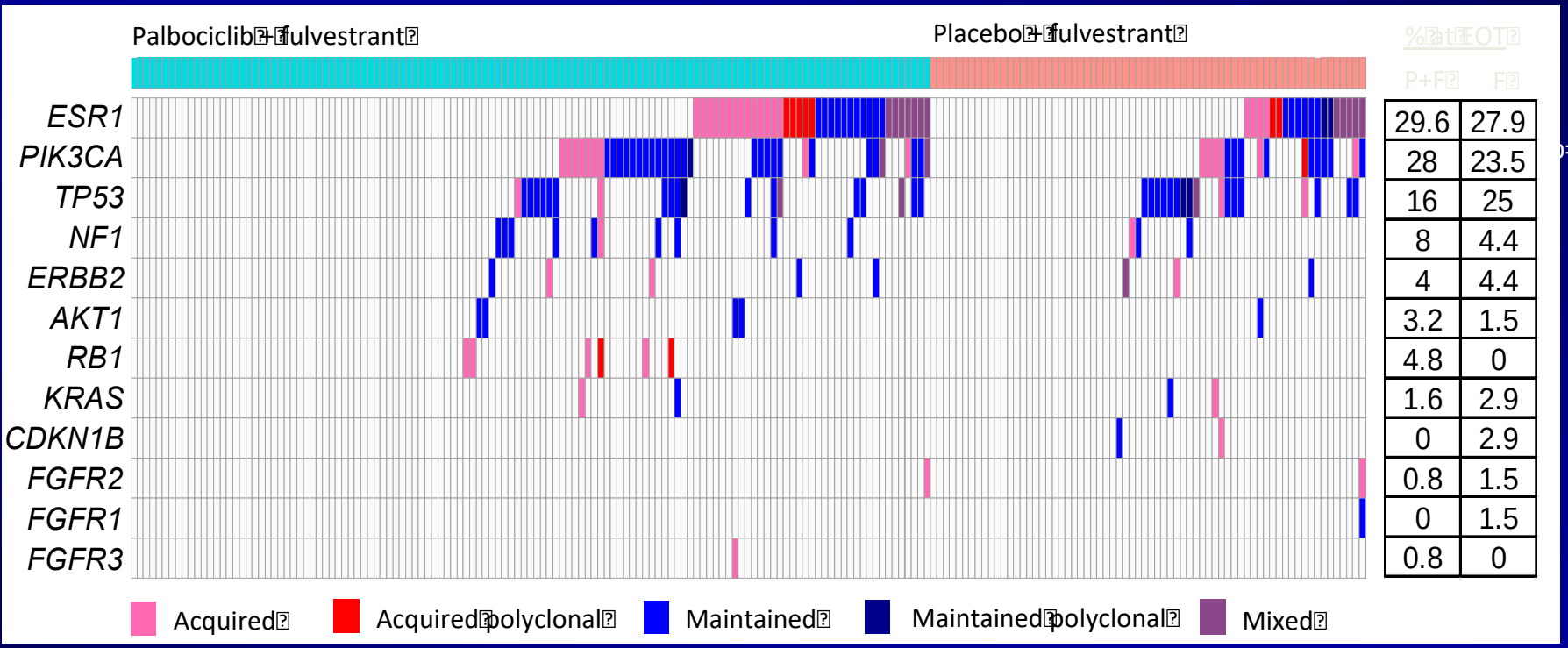



| PIK3CA mutation | Median PFS (mos) | 95% CI |
|---|---|---|
| No | 9.7 | 6.53 – 17.10 |
| Yes | 2.3 | 1.83 – 8.7 |

cfDNA may be a more accurate measure?

Rugo et al, AACR 2019

# PALOMA3 End of Treatment Driver Mutation Landscape




Patients with at least 1 acquired mutation(s): - 28.0% (35/125) palbociclib plus fulvestrant
- 22.1% (15/68) fulvestrant alone

O'Leary et al, Cancer Discovery 2018

# Future Steps (examples)

- Improving response
  - Fulvestrant vs AI plus CDK 4/6i (Parsifal, 486 pts)
  - CDK 4/6i after progression on CDK 4/6i (multiple trials)
- Understanding and reversing resistance
  - CDK 4/6i plus PI3Ki (limited by toxicity)
  - CDK 4/6i plus combined inhibitors (mTOR and PI3Ki, others)
  - CDK 4/6i plus mTORi
  - CDK 4/6i plus FGFRi
  - CDK 4/6i plus checkpoint inhibition
- > 100 active studies on clinicaltrials.gov: early stage as the next frontier!

Barve et al; Forero et al, Rugo et al, SABCS 2017, Tolaney et al, ASCO 2018, Goel et al, Nature 2017

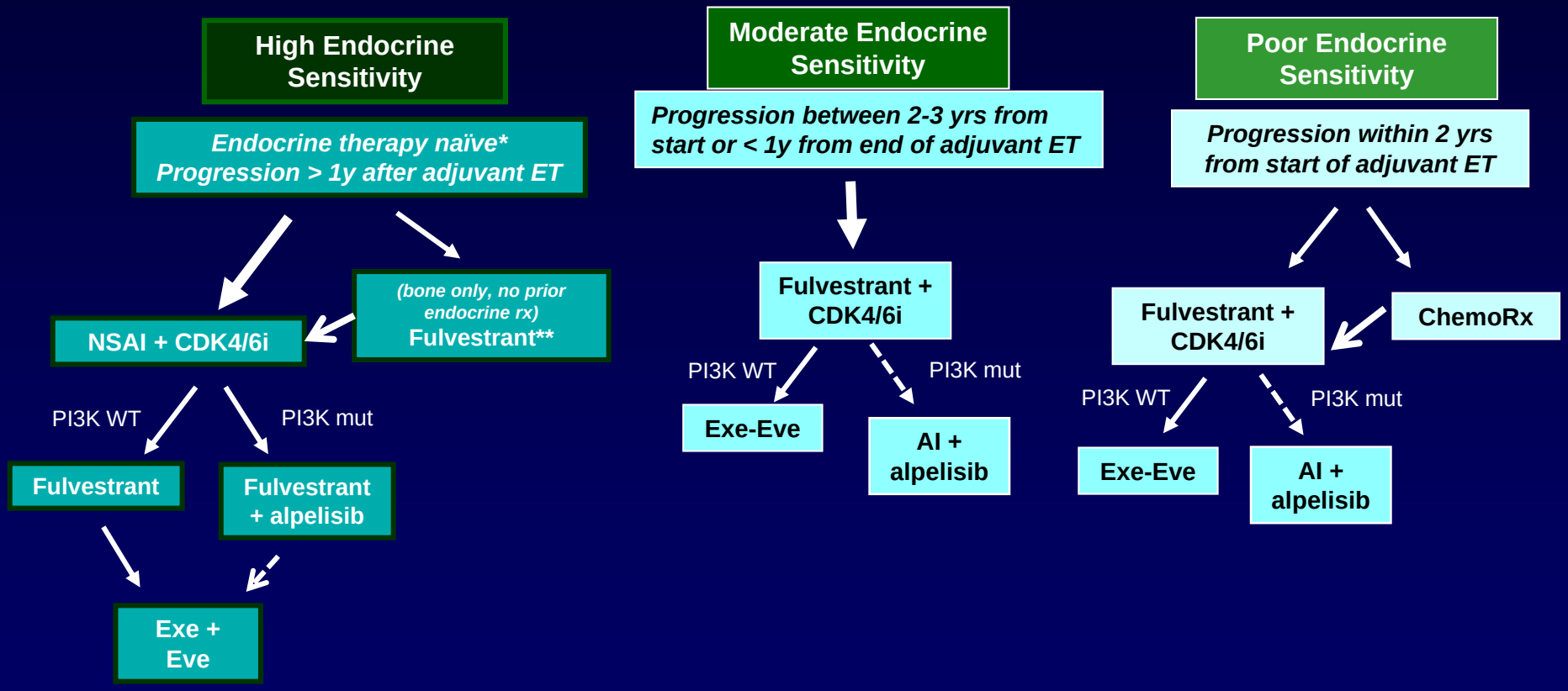
# Early Stage Disease

- **Post-neoadjuvant high risk**
  - **Penelope trial (n=1250)**
  - **Accrual completed**
- **Adjuvant**
  - **All focus on very high risk early stage HR+ BC**
    - **PALLAS** ***(n=5600, includes stage IIa, 2 years, accrual completed)***
    - **monarchE** ***(n=4580, 2 years, accrual completed)***
    - **NataLEE** ***(n=4000; 3 years, newly open 2018)***

# Algorithm?

- Ever changing!
  - >12 months post adjuvant AI/denovo metastatic disease: AI+CDK 4/6i
  - ≤12 months or intolerant of AI: Fulvestrant + CDK 4/6i
- What treatment after progression?
  - ESR1 mutation: fulvestrant with or without eve instead of exe/eve
  - Mutation based therapy?
    - PI3K inhibitor alpeslib for those with PI3K mutations
  - Beware acquired mutations and loss of ER with progression
- Who doesn't need CDK4/6i as initial therapy?
  - de novo limited bone only or soft tissue disease, very elderly with limited bone disease and endocrine sensitivity?
  - Need to have access to CDK 4/6i as second line therapy!

# HR+HER2- ABC: Changing Paradigms




*De novo stage IV disease appears to be enriched in relative endocrine resistant disease*

***No data comparing CDK4/6i combined with AI vs fulvestrant in the first line setting*


Raising the Bar in the Treatment of Hormone Responsive Advanced Breast Cancer
Thank you!