# Giuseppe Curigliano

Department of Oncology and Hematology
University of Milano
Istituto Europeo di Oncologia
Milano, Italy

# Strategie Terapeutiche nel Carcinoma Mammario Metastatico: Il punto di vista del Clinico

# Disclosures

Grants: Associazione Italiana Ricerca sul Cancro, MSD, Italian Minister of Health

Personal fees: Astra Zeneca, Pfizer, Roche/Genentech, Novartis

# Outline

- Endocrine therapy plus CDK 4-6 inhibitors as a new standard of care for HR+/HER2- advanced breast cancer
- Endocrine sensitive and endocrine resistant disease
- The PALOMA programs
- Overview of data from MONALEESA and MONARCH programs
- Positioning of CDK 4-6 inhibitors in standard clinical practice

# Top line recommendations from ESO-ESMO ABC4 panel

"**Endocrine therapy** is the **preferred option** for hormone receptor positive disease, even in the presence of visceral disease, unless there is visceral crisis or concern/proof of endocrine resistance"



Cardoso F, *et al. Annals of Oncology*. 2018

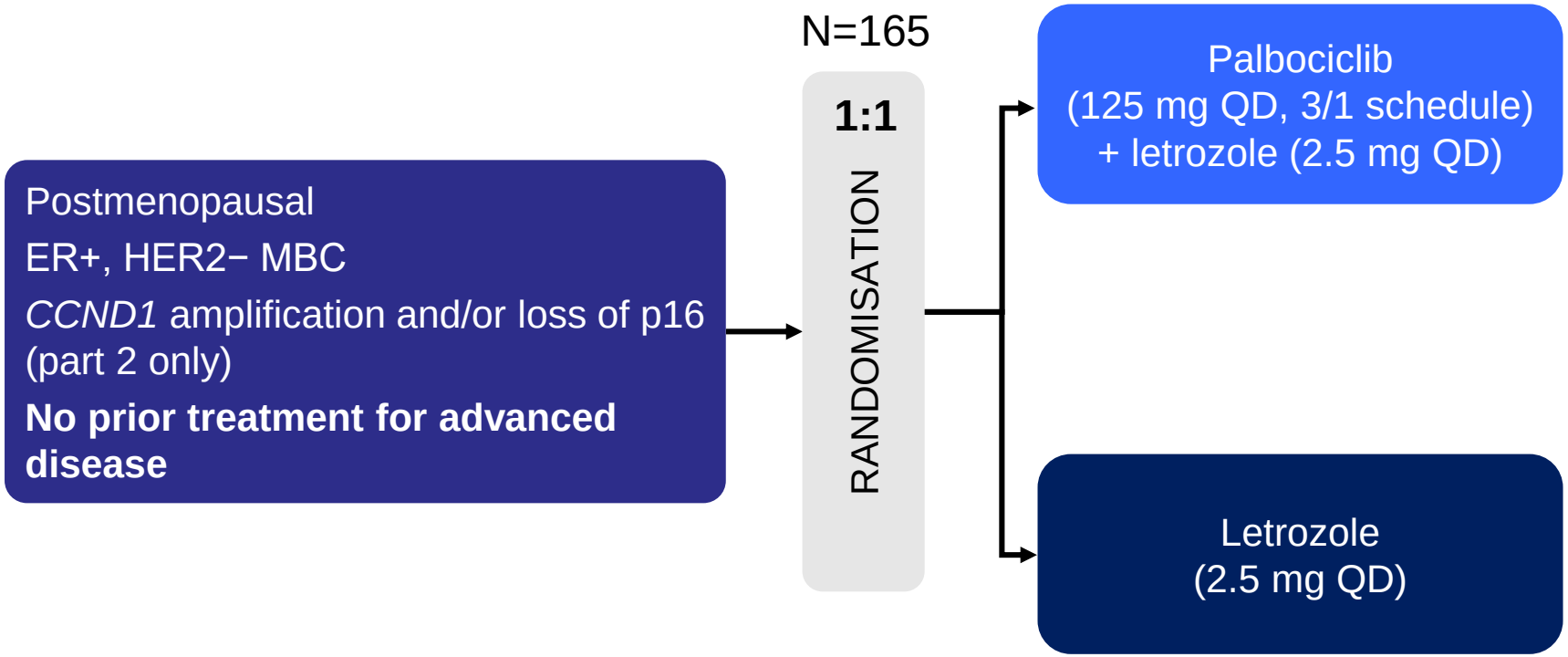
# The PALOMA trials

| Trial | Study design | Study size | Target population HR+/HER2– mBC | Partner ET | Primary endpoint |
|---|---|---|---|---|---|
| PALOMA-1 | Phase 2<br>Open label | 165 patients | AI sensitive<br>Treatment naïve for mBC<br>Postmenopausal | Letrozole | PFS |
| PALOMA-2 | Phase 3<br>Placebo control | 666 patients | AI sensitive<br>Treatment naïve for mBC<br>Postmenopausal | Letrozole | PFS |
| PALOMA-3 | Phase 3<br>Placebo control | 521 patients | Endocrine resistant<br>Pre/peri and postmenopausal | Fulvestrant | PFS |

- PFS, progression free survival

Finn RS, *et al. Lancet Oncol.* 2015;16:25–35; Finn RS, *et al. N Engl J Med.* 2016;375:1925–1936; Turner NC, *et al. N Engl J Med*. 2015;373:209–219; Cristofanilli M, *et al. Lancet Oncol*. 2016;17:425–439.

# PALOMA-1: Phase II study design




**Primary endpoint: progression-free survival**

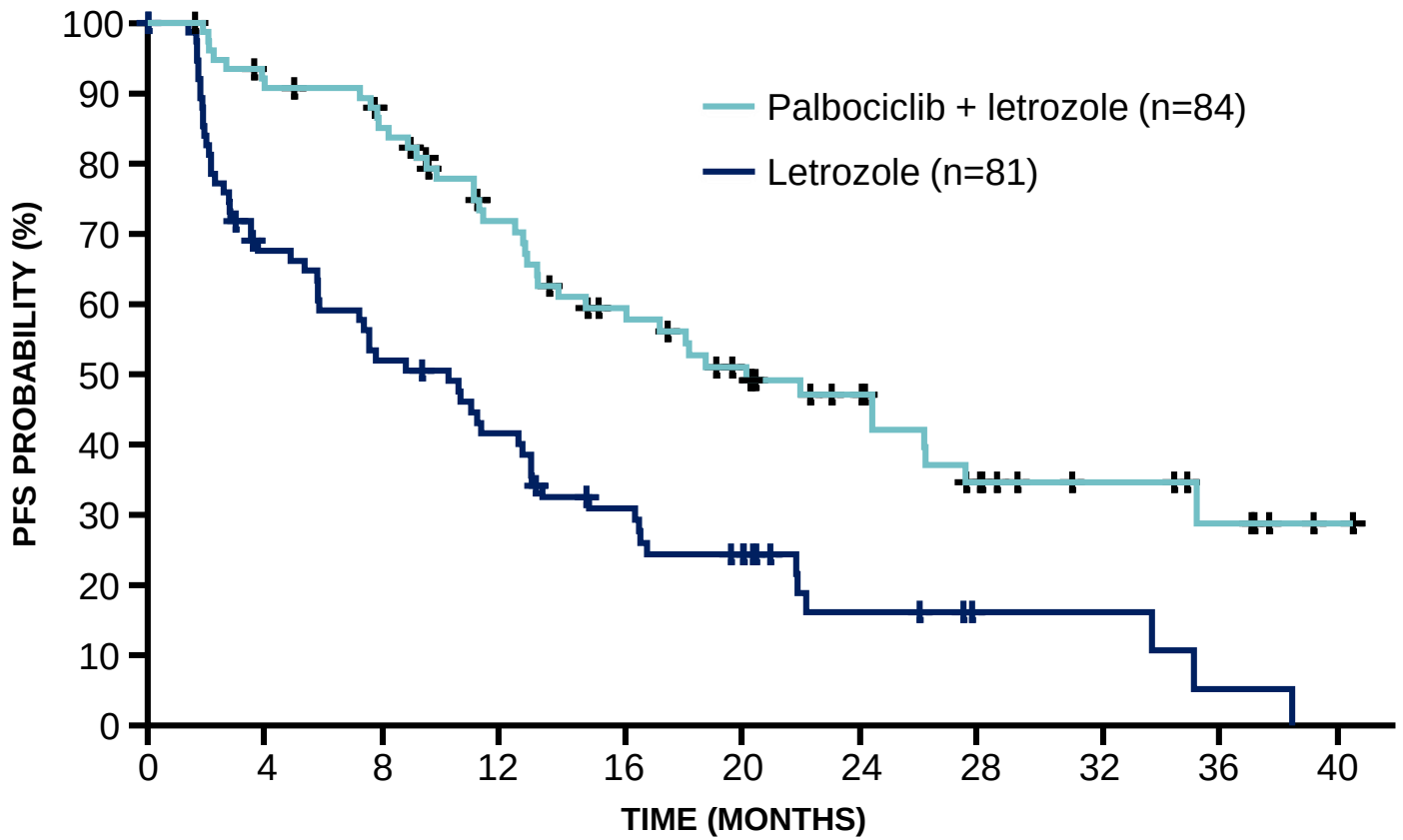
Secondary/exploratory endpoints: response, overall survival, safety, biomarkers, patient-reported outcomes

Stratification factors: disease site, disease-free interval

- HER2, human epidermal growth factor receptor 2; QD, once daily

Finn RS, *et al. Lancet Oncol*. 2015;16:25–35.

# PALOMA-1: Progression free survival




Number of patients at risk

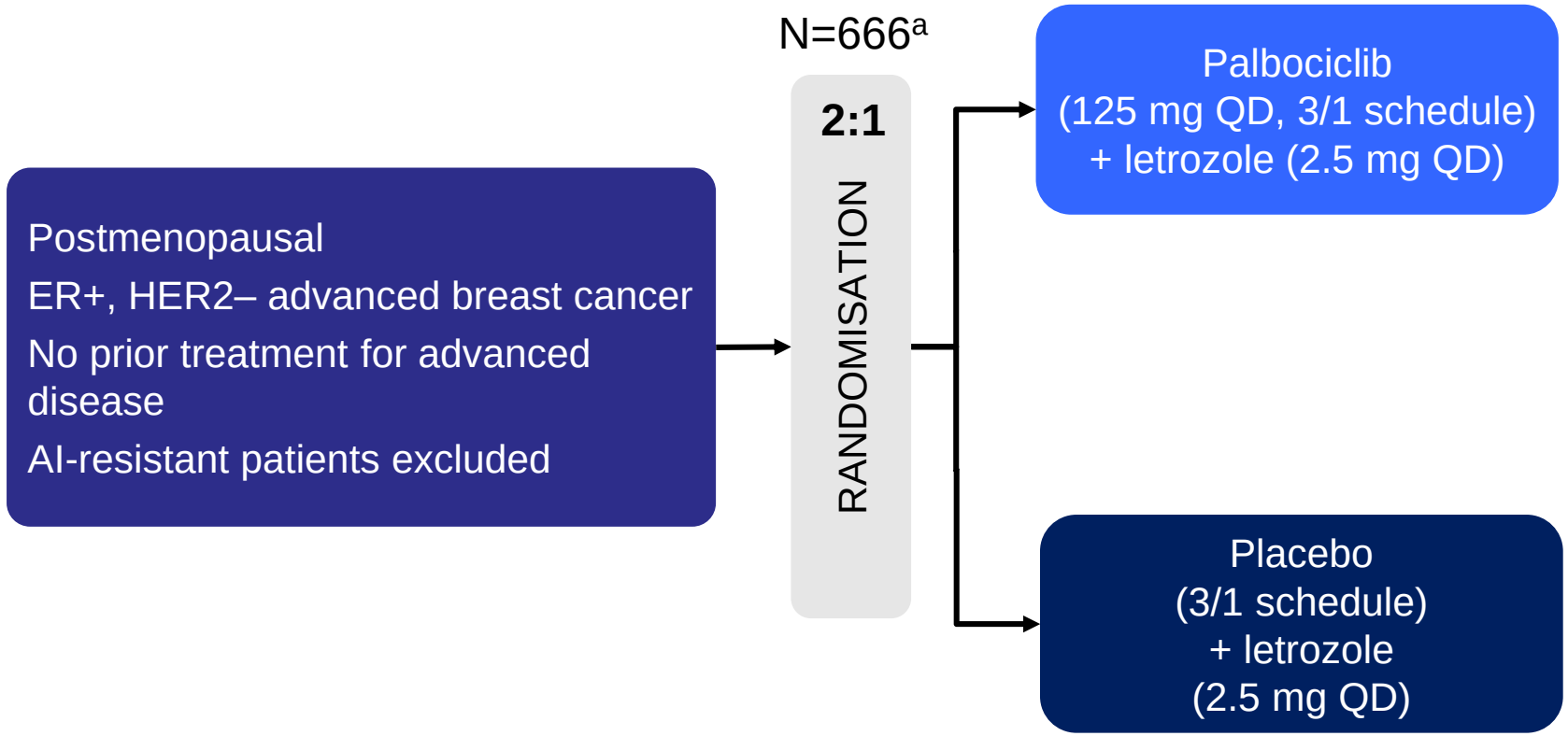
| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PAL+LET | 84 | 67 | 60 | 47 | 36 | 28 | 21 | 13 | 8 | 5 | 1 |
| LET | 81 | 48 | 36 | 28 | 19 | 14 | 6 | 3 | 3 | 1 | |

| | PAL + LET (n = 84) | LET (n = 81) |
|---|---|---|
| Number of events (%) | 41 (49) | 59 (73) |
| Median PFS, months (95% CI) | 20.2 (13.8–27.5) | 10.2 (5.7–12.6) |
| HR (95% CI) | 0.488 (0.319–0.748) | |
| P value | 0.0004 | |

**Accelerated approval by FDA**

- HR, hazard ratio; LET, letrozole; PAL, palbociclib; PFS, progression-free survival
- Finn RS, *et al. Lancet Oncol*. 2015;16:25–35.
- FDA US Food and Drug Administration; www.FDA.gov.

# PALOMA-2: Phase III study design




**Primary endpoint**
**Investigator-assessed PFS**

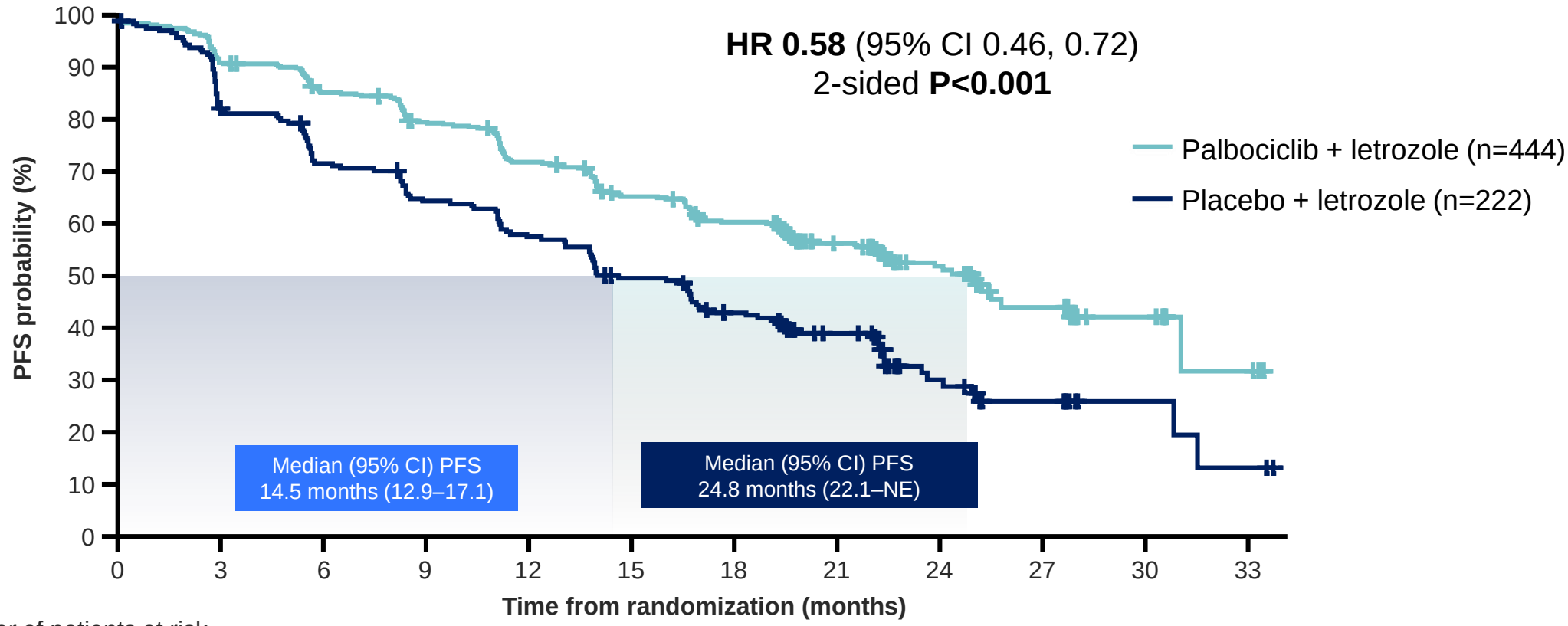
Secondary endpoints include: Response, OS, safety, biomarkers, patient-reported outcomes

Stratification factors
- Disease site (visceral, non-visceral)
- Disease-free interval (de novo metastatic; ≤12 mo, >12 mo)
- Prior (neo)adjuvant hormonal therapy (yes, no)

- [a]Actual.
- AI, aromatase inhibitor; OS, overall survival; PFS, progression-free survival; QD, once daily

Finn RS, *et al. N Engl J Med.* 2016;375:1925–1936.

# PALOMA-2: Progression free survival



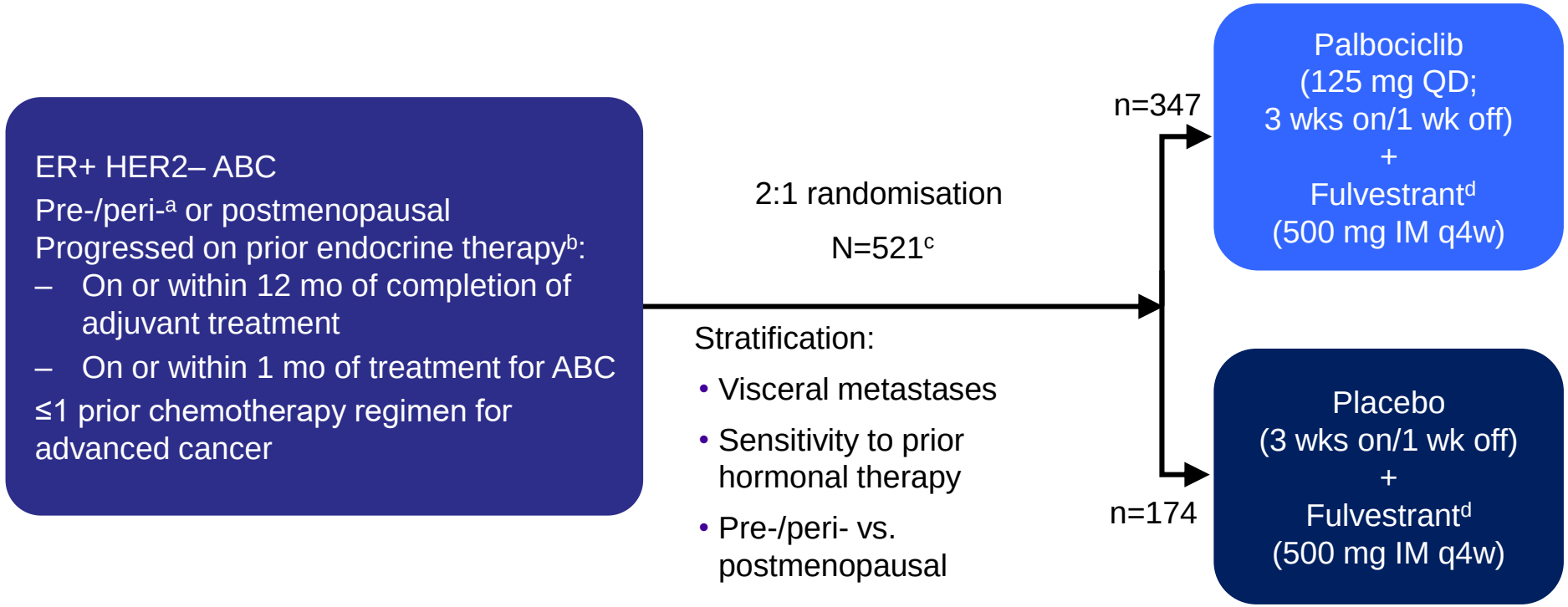

Number of patients at risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PAL+LET | 444 | 395 | 360 | 328 | 295 | 263 | 238 | 154 | 69 | 29 | 10 | 2 |
| PCB+LET | 222 | 171 | 148 | 131 | 116 | 98 | 81 | 54 | 22 | 12 | 4 | 2 |

HR, hazard ratio; LET, letrozole; NE, not estimable; PAL, palbociclib; PCB, placebo; PFS, progression-free survival

Finn RS, *et al. N Engl J Med.* 2016;375:1925–1936.

# PALOMA-3: Phase III study design




## Randomised Phase III double-blind trial at 144 centres in 17 countries

[a]All received goserelin.

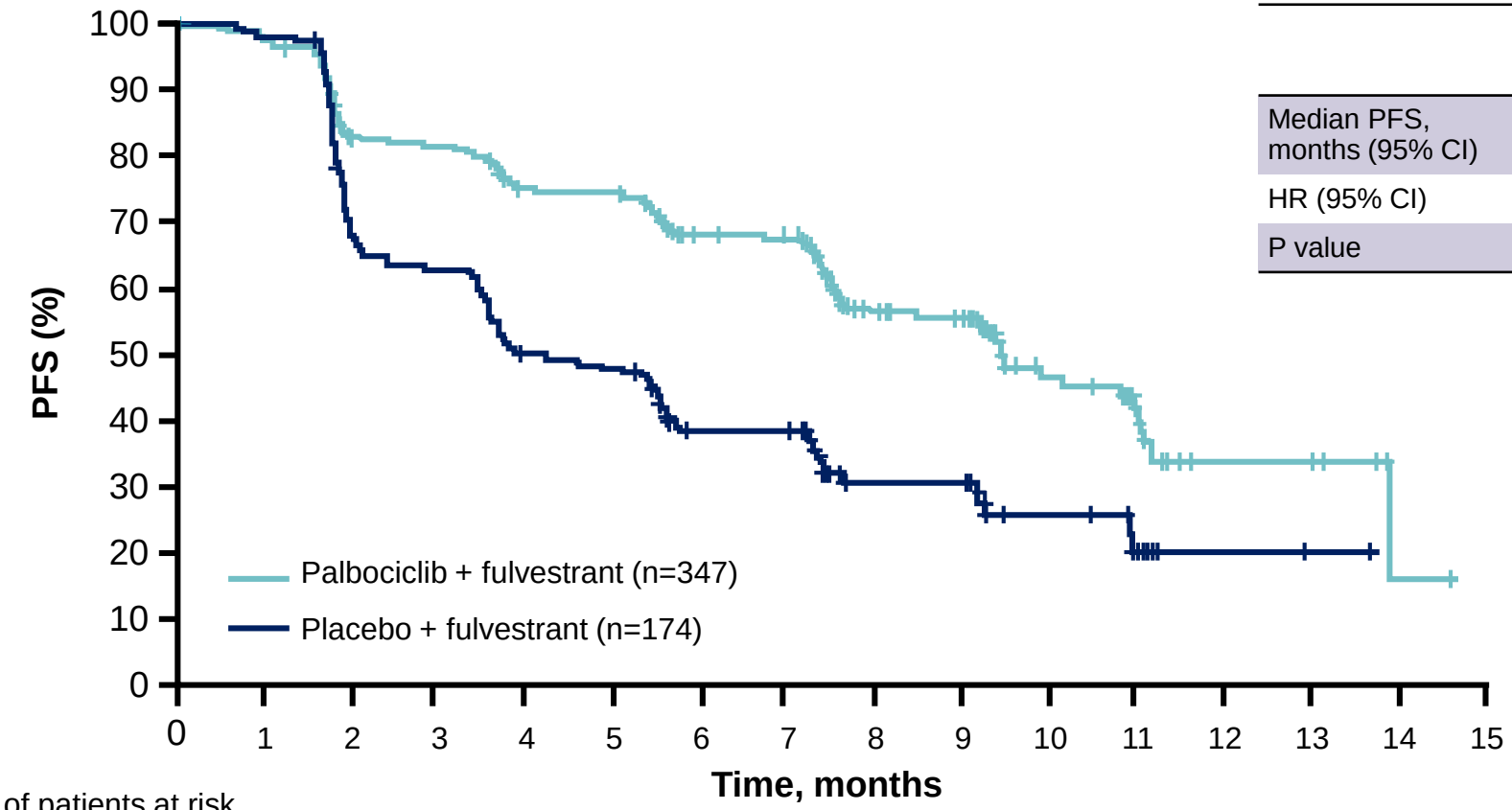
[b]Must have progressed on prior endocrine therapy (pre-/perimenopausal) or aromatase inhibitor therapy (postmenopausal).

[c]Patients randomised. [d]Administered on Days 1 and 15 of Cycle 1, then every 28 d.

HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; q4w, every 4 weeks; QD, once daily

Turner NC, *et al. N Engl J Med*. 2015;373:209–219;
Cristofanilli M, *et al. Lancet Oncol*. 2016;17:425–439.

# PALOMA-3 update: Investigator-assessed PFS




| | PAL + FUL (n=347) | PBO + FUL (n=174) |
|---|---|---|
| Median PFS, months (95% CI) | 9.5 (9.2–11.0) | 4.6 (3.5–5.6) |
| HR (95% CI) | 0.46 (0.36–0.59) | |
| P value | <0.0001 | |

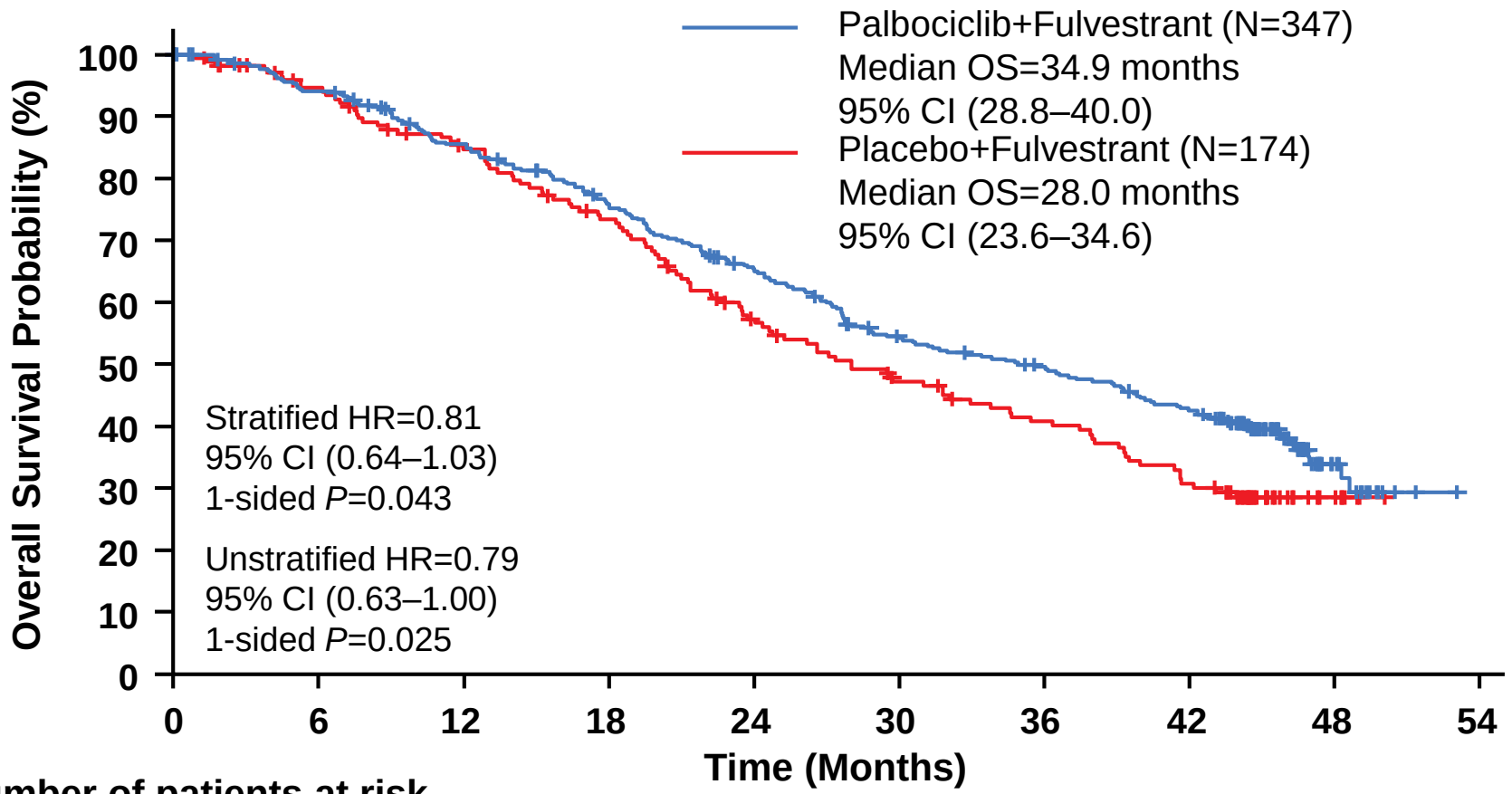
Number of patients at risk

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PAL + FUL | 347 | 333 | 281 | 273 | 247 | 244 | 202 | 197 | 91 | 85 | 32 | 23 | 7 | 7 | 1 | 0 |
| PBO + FUL | 174 | 165 | 112 | 105 | 83 | 80 | 59 | 58 | 22 | 22 | 13 | 7 | 2 | 1 | 0 | 0 |

FUL, fulvestrant; NE, not estimable; PAL, palbociclib; PBO, placebo; PFS, progression-free survival


Turner NC, *et al. N Engl J Med*. 2015;373:209–219;
Cristofanilli M, *et al. Lancet Oncol*. 2016;17:425–439.

# OVERALL SURVIVAL IN PALOMA-3 (ITT)



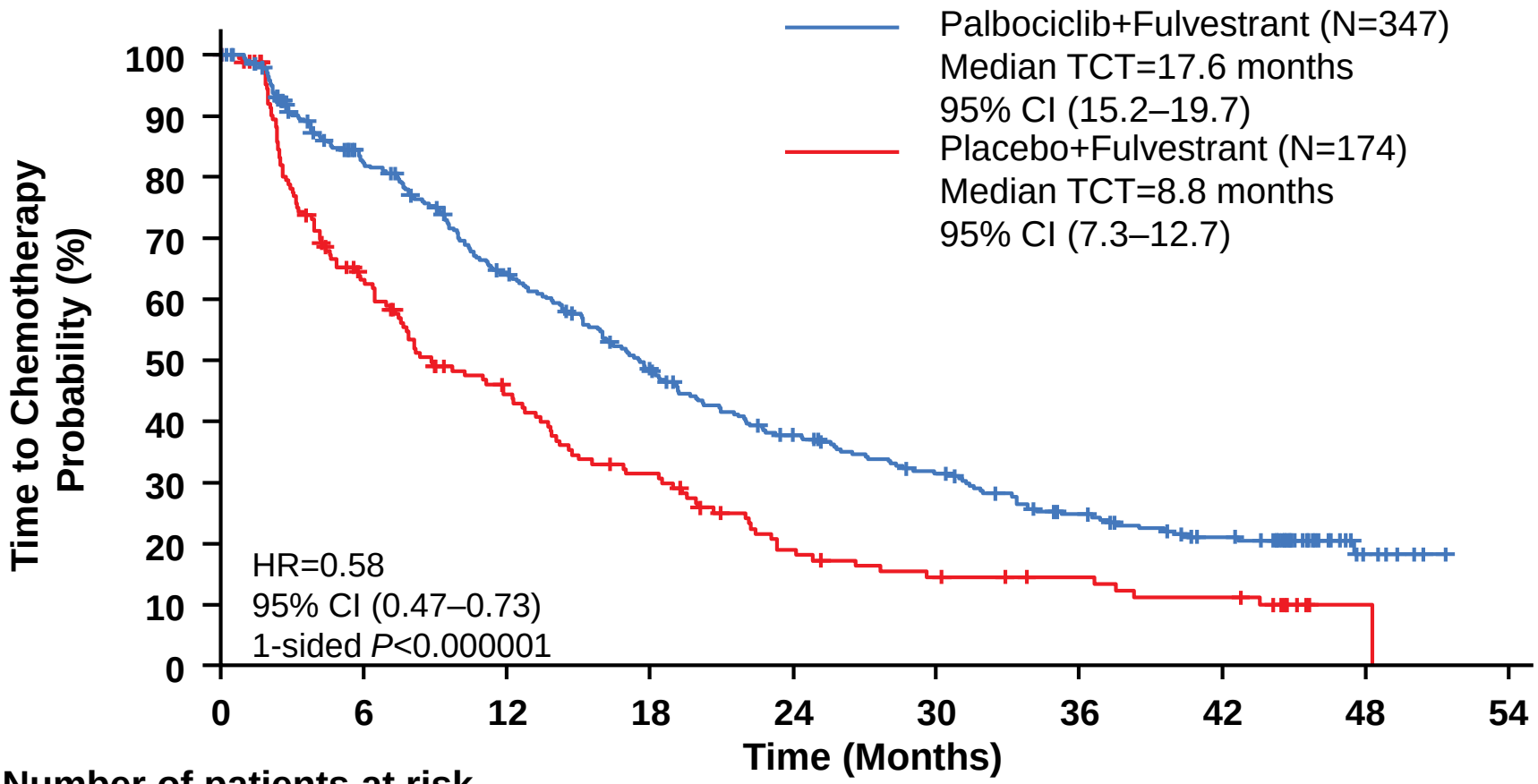

**Number of patients at risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **PAL+FUL** | 347 | 321 | 286 | 247 | 209 | 165 | 148 | 126 | 17 |
| **PBO+FUL** | 174 | 155 | 135 | 115 | 86 | 68 | 57 | 43 | 7 |

FUL=fulvestrant;
HR=hazard ratio;
ITT=intent-to-treat;
PAL=palbociclib;
PBO=placebo.

- **Absolute improvement in median OS in the palbociclib arm versus the placebo arm was 6.9 months.**

# TIME FROM RANDOMIZATION TO START OF POSTPROGRESSION CHEMOTHERAPY




**Number of patients at risk**

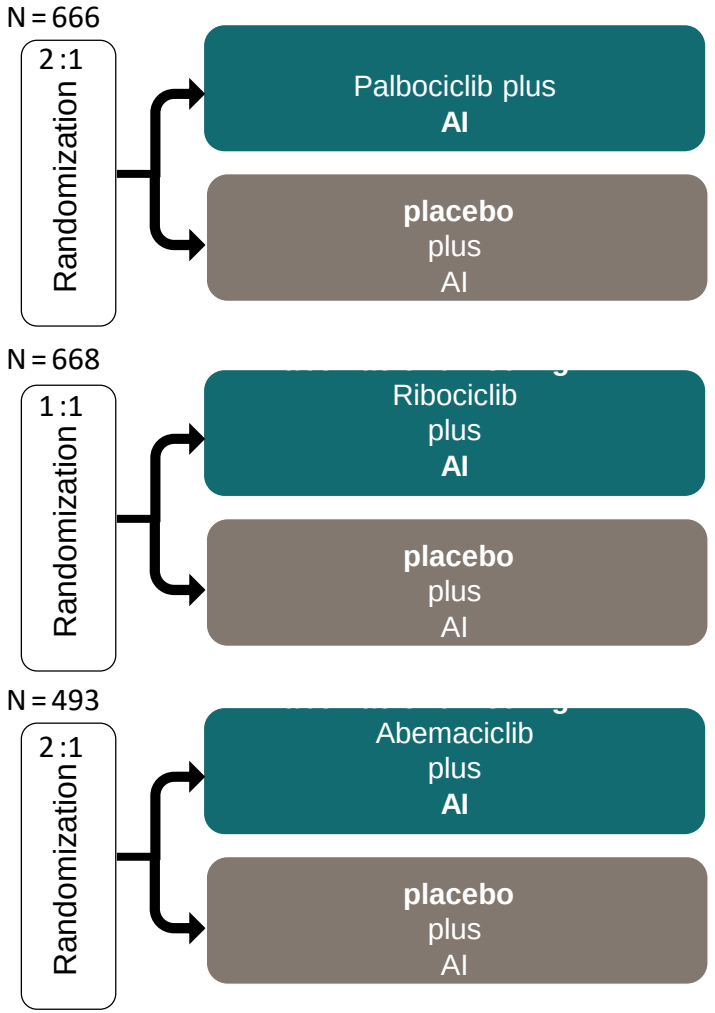
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **PAL+FUL** | 347 | 254 | 182 | 133 | 99 | 78 | 56 | 41 | 6 |
| **PBO+FUL** | 174 | 91 | 58 | 40 | 22 | 16 | 13 | 10 | 1 |

TCT= time to chemotherapy.

# Endocrine sensitive disease: 1st line

- HR+, HER2- ABC
- Postmenopausal
- Noprior systemic therapy in this setting
- If neoadjuvant or adjuvant ET administered, a disease free interval of >12 months since completion of ET
- ECOG PS ≤1

**Primary endpoint:**
Investigator-assessed PFS




**PALOMA-2[1]**

**MONALEESA-2[2]**

**MONARCH-3[3]**

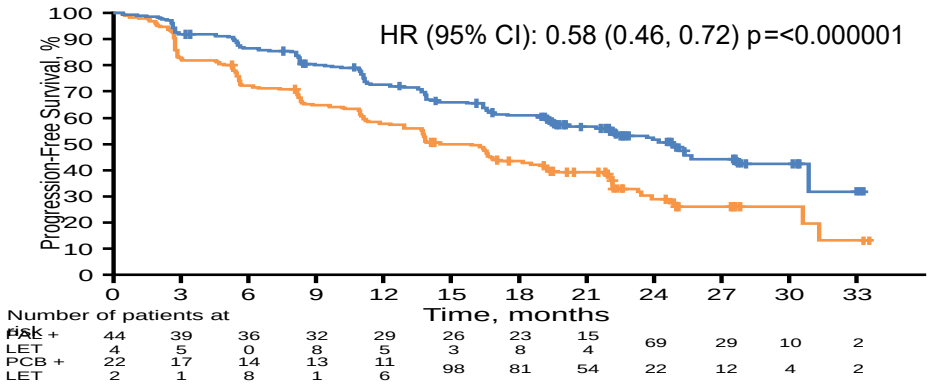
[1]Finn RS, et al. N Engl J Med 2016; [2]Hortobagyi G, et al. N Engl J Med 2016; [3]di Leo A, et al. J Clin Oncol 2017

# Endocrine sensitive disease

**PALOMA 2 (2:1)**

Median PFS
**Palbociclib + NSAI:** 24.8 m
**placebo + NSAI:** 14.5 m

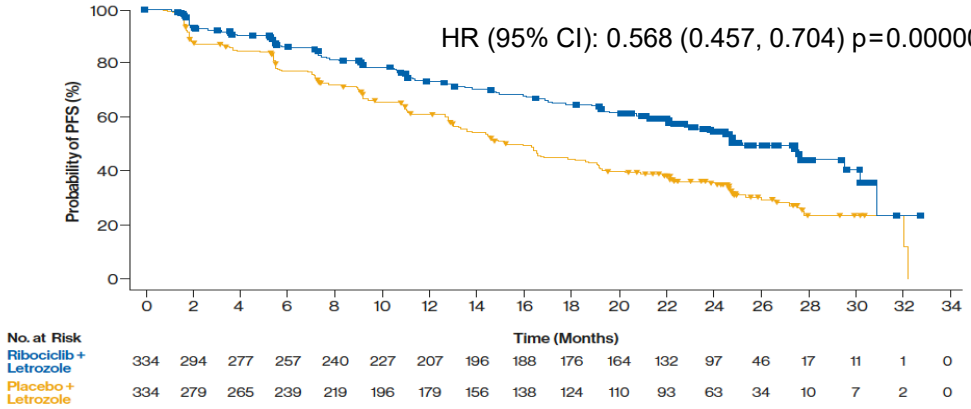
HR (95% CI): 0.58 (0.46, 0.72) p=<0.000001

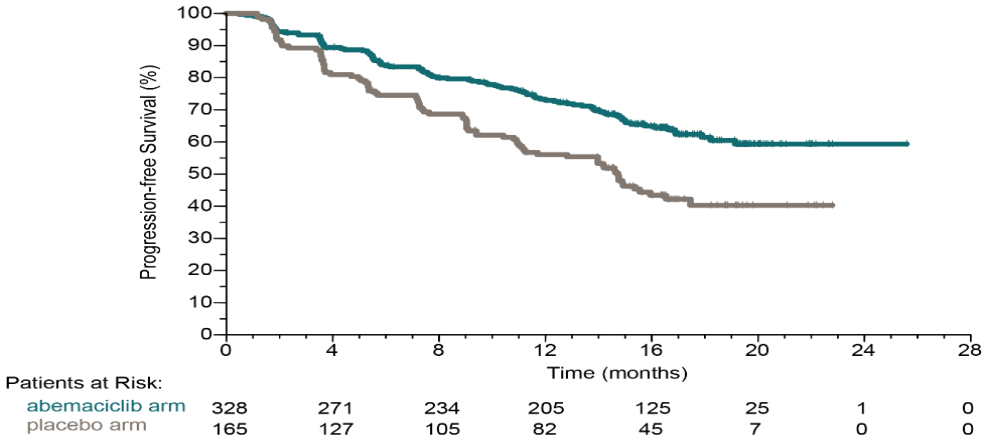



**MONALEESA 2 (1:1)**

Median PFS
**Ribociclib + NSAI:** 25.3 m
**placebo + NSAI:** 16 m

HR (95% CI): 0.568 (0.457, 0.704) p=0.000000096



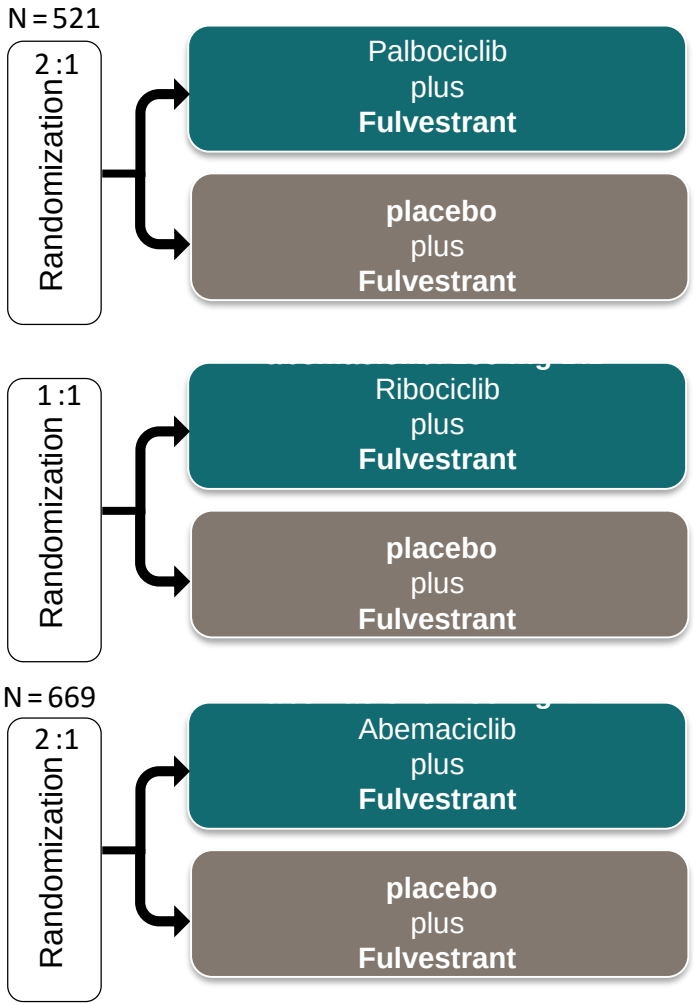

**MONARCH 3 (2:1)**

Median PFS
**abemaciclib + NSAI:** not reached
**placebo + NSAI:** 14.7 m

HR (95% CI): 0.543 (0.409, 0.723) p=0.000021

# Endocrine resistant disease: 1st line

- ER+, HER2- ABC
- Pre/peri & Postmenopausal*
- Progressed on prior endocrine therapy:
  - –On or within 12 mo adjuvant
  - –On therapy for ABC




**Primary endpoint:**
Investigator-assessed PFS

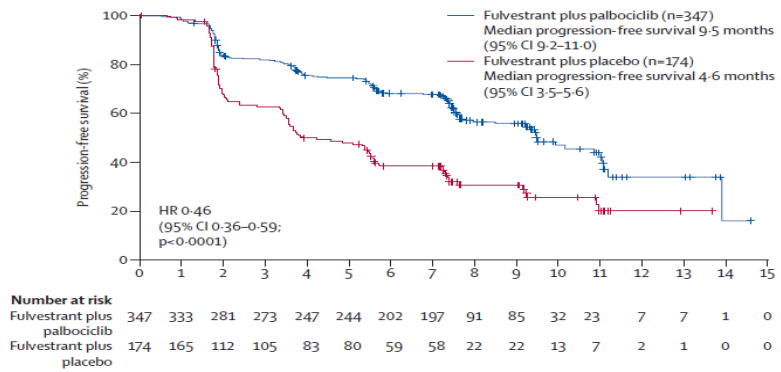
*Only postmenopausal

[1]Turner NC, et al. N Engl J Med 2015; [2]Slamon D et al, J Clin Oncol 2018; [3]Sledge G, et al. J Clin Oncol 2017

# Endocrine resistant disease

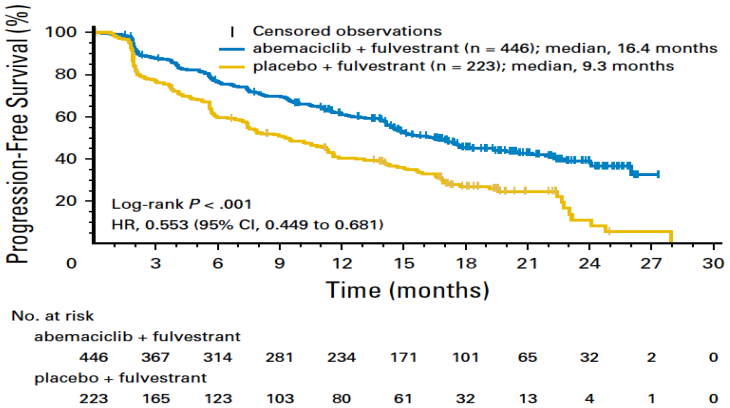
## PALOMA 3[1,2]

HR (95% CI): 0.46 (0.36, 0.59)
p=<0.0001



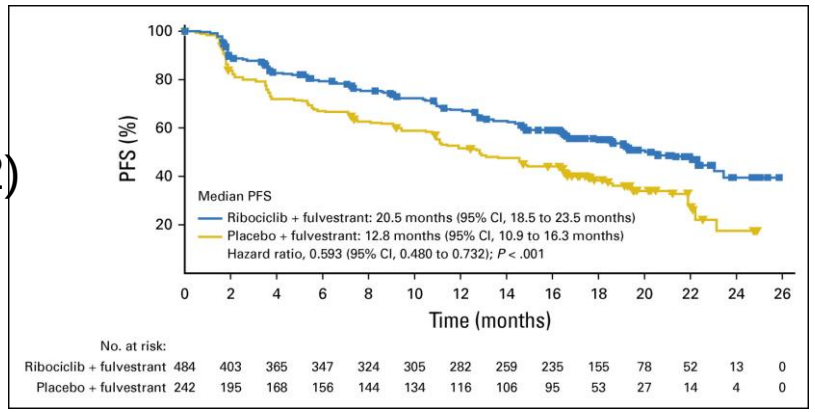

## MONARCH2[3]

HR (95% CI): 0.55 (0.45, 0.68)
p=<0.001




## MONALEESA 3[4]

HR (95% CI): 0.593 (0.480, 0.732)
p=<0.001




[1]Turner NC, et al. N Engl J Med 2015; [2]Cristofanilli M, et al. Lancet Oncol 2016;
[3]Sledge G, et al. J Clin Oncol 2017, [4]Slamon D et al, J Clin Oncol 2018

# STUDY DESIGN MONARCH-2 N=669

- HR+/HER2- ABC
- Pre/peri-[a] or postmenopausal
- ET resistant:
  - Relapsed on neoadjuvant or on/within 1 yr of adjuvant ET
  - Progressed on first-line ET for ABC
- No chemo for ABC
- No more than 1 ET for ABC
- ECOG PS ≤ 1

2:1 Randomization

**Abemaciclib:** 150 mg[b] BID (continuous schedule)
**fulvestrant:** 500 mg[c]

**placebo:** BID (continuous schedule)
**fulvestrant:** 500 mg[c]

**Primary endpoint:**
Investigator-assessed PFS

**Secondary endpoint:**
Overall survival

**Exploratory endpoints:**
Time to chemotherapy (TTC)

**Stratification factors:**

- Metastatic site (visceral, bone only, or other)
- ET resistance (primary or secondary)[7,8]

- Data cut-off: 20 June 2019
- Median follow-up: 47.7 months

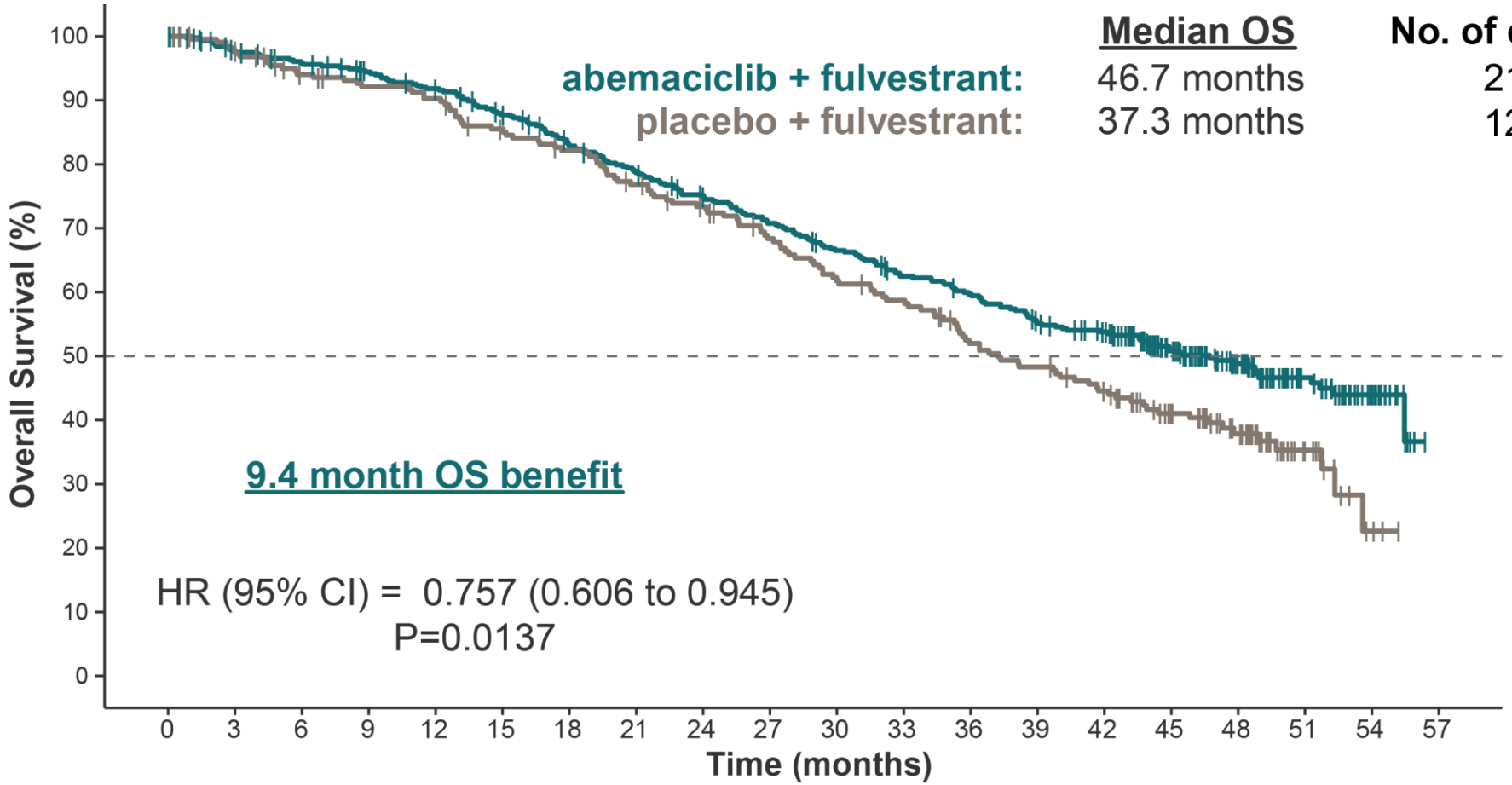
[a]Required to receive GnRH agonist
[b]Dose reduced by protocol amendment in all new and ongoing patients from 200 mg to 150 mg BID after 178 patients enrolled
[c]Fulvestrant administered per label

Sledge G et al. ESMO 2019 LBA



[7]Cardoso et al. *Breast.* 2017;35:203-217; [8]Cardoso et al. *Ann Oncol.* 2017;28(12):3111

# OVERALL SURVIVAL MONARCH-2




No. at risk

| | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| abemaciclib + fulvestrant | 446 | 422 | 410 | 397 | 384 | 364 | 339 | 321 | 302 | 284 | 265 | 246 | 234 | 214 | 202 | 157 | 101 | 58 | 23 | 0 |
| placebo + fulvestrant | 223 | 214 | 201 | 195 | 191 | 178 | 170 | 158 | 148 | 135 | 122 | 115 | 99 | 92 | 82 | 62 | 42 | 15 | 3 | 0 |

# MONALEESA-3 Study Design

Men and postmenopausal women with HR+/HER2− ABC

≤ 1 line of prior ET for advanced disease

N = 726

Randomized 2:1

**Stratified by:**
- Presence/absence of liver/lung metastases
- Prior endocrine therapy

**Ribociclib**
(600 mg/day;
3 weeks on/1 week off)
+
fulvestrant
(500 mg)[a]
n = 484

**Placebo**
+
fulvestrant
(500 mg)[a]
n = 242

**Primary end point**
- PFS (locally assessed per RECIST version 1.1)

**Secondary end points**
- Overall survival
- Overall response rate
- Clinical benefit rate
- Time to response
- Duration of response
- Time to definitive deterioration of ECOG PS
- Patient-reported outcomes
- Safety
- Pharmacokinetics

## Patient population definitions

Treatment naive for ABC
- TFI > 12 mo
- De novo ABC

≤ 1 line ET in ABC
- TFI ≤ 12 mo and no treatment for ABC = early relapse
- TFI > 12 mo + PD on 1L ET for ABC
- ABC at diagnosis with PD on 1L ET for ABC

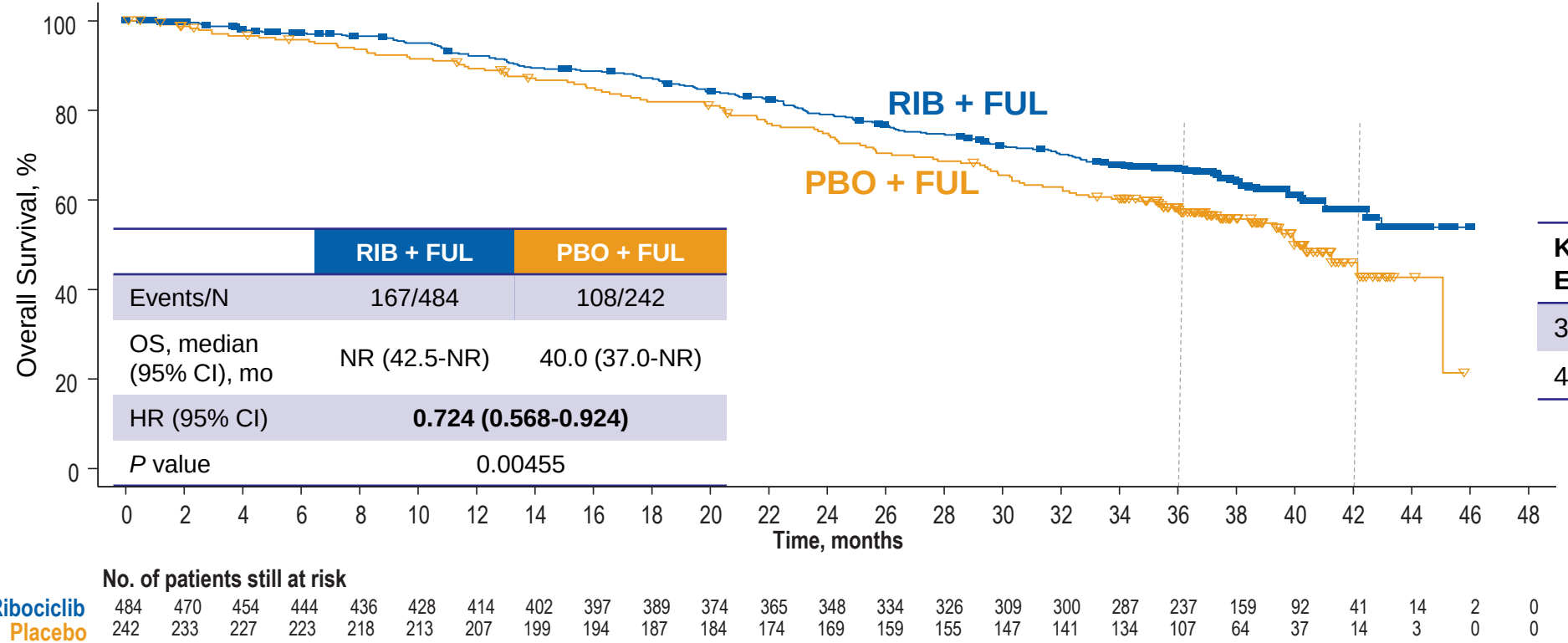
1L, first line; 2L, second line; ABC, advanced breast cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TFI, treatment-free interval.

Slamon DJ, et al. *J Clin Oncol*. 2018;36:2465-247.

Slamon D et al. ESMO 2019 LBA

# Overall Survival MONALEESA-3

## *The relative reduction in risk of death with RIB was 28%*




| | RIB + FUL | PBO + FUL |
|---|---|---|
| Events/N | 167/484 | 108/242 |
| OS, median (95% CI), mo | NR (42.5-NR) | 40.0 (37.0-NR) |
| HR (95% CI) | **0.724 (0.568-0.924)** | |
| *P* value | 0.00455 | |

**No. of patients still at risk**

| | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ribociclib | 484 | 470 | 454 | 444 | 436 | 428 | 414 | 402 | 397 | 389 | 374 | 365 | 348 | 334 | 326 | 309 | 300 | 287 | 237 | 159 | 92 | 41 | 14 | 2 | 0 |
| Placebo | 242 | 233 | 227 | 223 | 218 | 213 | 207 | 199 | 194 | 187 | 184 | 174 | 169 | 159 | 155 | 147 | 141 | 134 | 107 | 64 | 37 | 14 | 3 | 0 | 0 |

**Landmark Analysis**

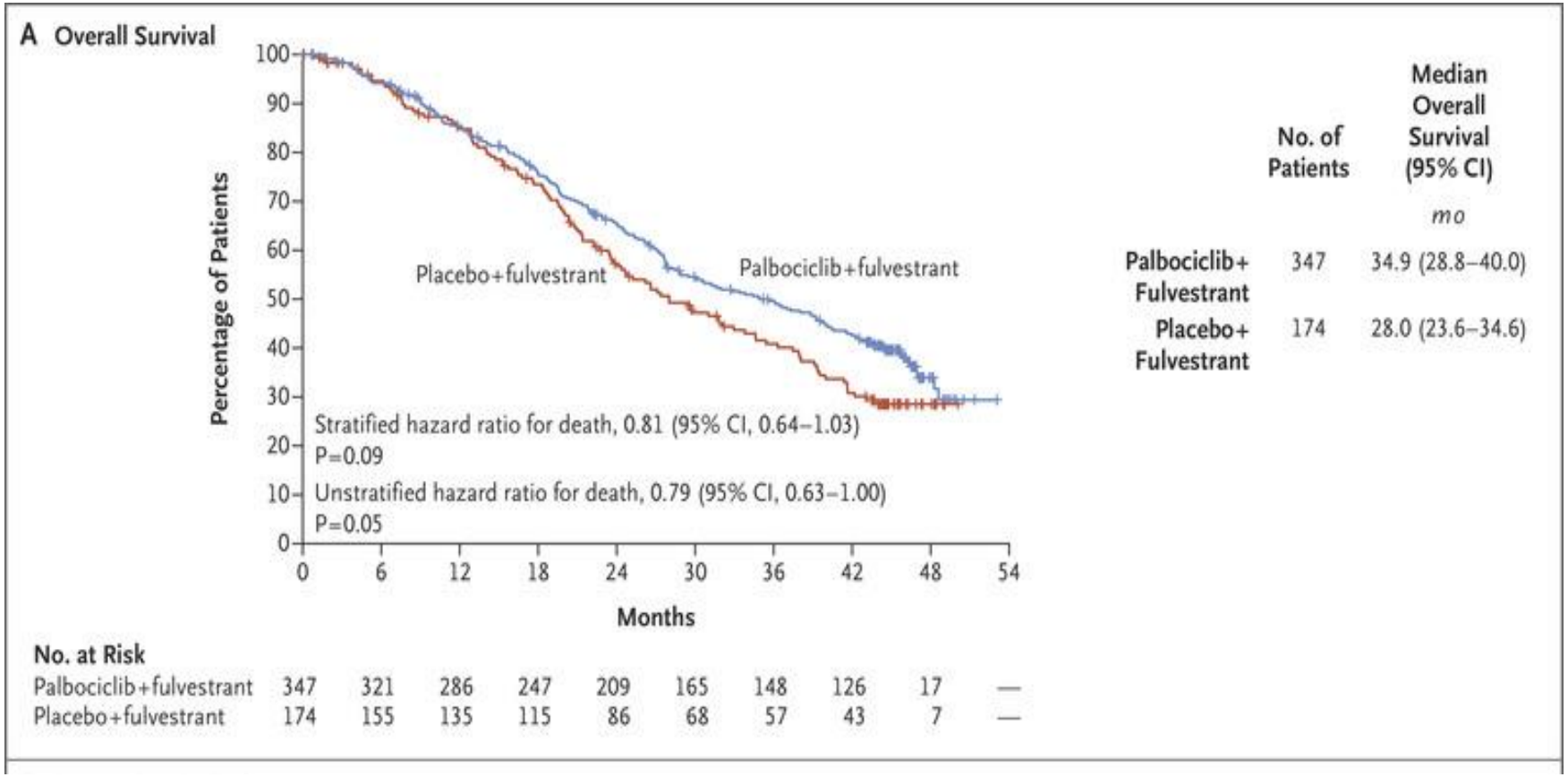
| KM Estimate | RIB + FUL | PBO + FUL |
|---|---|---|
| 36 months | 67.0% | 58.2% |
| 42 months | 57.8% | 45.9% |

- The *P* value of 0.00455 crossed the prespecified boundary to claim superior efficacy (*P* < 0.01129)

FUL, fulvestrant; HR, hazard ratio; KM, Kaplan-Meier; NR, not reached; OS, overall survival; PBO, placebo; RIB, ribociclib.

Slamon D et al. ESMO 2019 LBA

# PALOMA 3 Overall Survival Analysis N=521



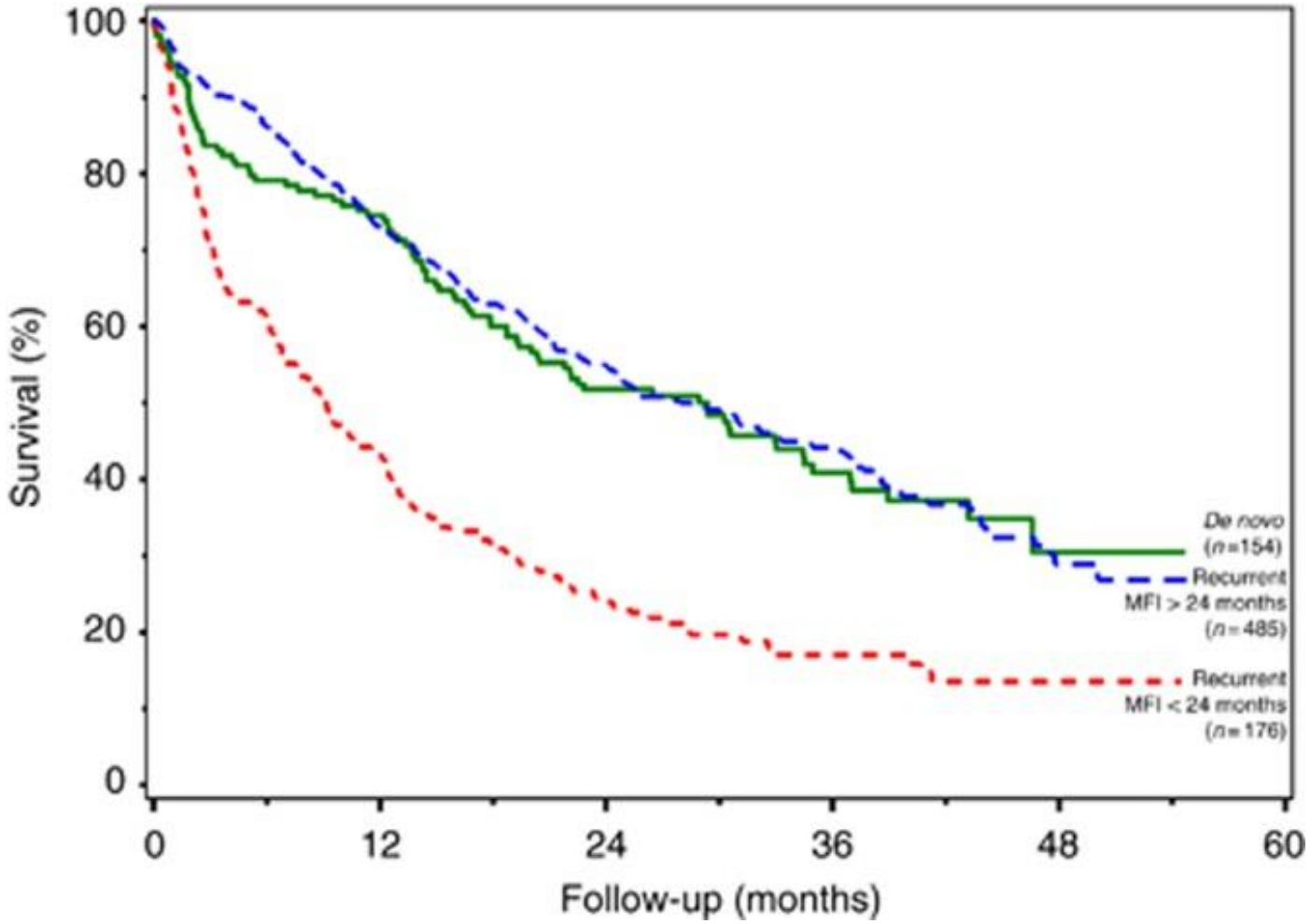

Turner N et al. New Engl J 2018

# Patient populations in PALOMA3, MONALEESA3 and MONARCH2

| | PALOMA3[1] N=521 | | MONALEESA3[2] N=726 | | MONARCH2[3] N=669 | |
|---|---|---|---|---|---|---|
| | Fulvestrant + palbociclib n (%) | Fulvestrant n (%) | Fulvestrant + ribociclib n (%) | Fulvestrant n (%) | Fulvestrant + abemaciclib n (%) | Fulvestrant n (%) |
| **ET inclusion criteria** | • **Progressed on or ≤12 months from prior adjuvant therapy with AI*/ tamoxifen**<br>• **Progressed on or ≤1 month from prior advanced breast cancer with AI*/ ET** | | • **First line (treatment naïve for ABC)**<br>• **Second line + early relapsers** | | • **Relapsed on neoadjuvant or on/within 1 year of adjuvant endocrine therapy**<br>• **Progressed on first line therapy** | |
| **Median age, years (range)** | 57 (30–88) | 56 (29–80) | 63 (31–89) | 63 (34–86) | 59 (32–91) | 62 (32–87) |
| **Most recent ET** | | | | | | |
| • **De novo†** | – | – | 97 (20%) | 42 (17.4%) | – | – |
| • **(neo)adjuvant setting** | 74 (21%)* | 40 (23%)* | 289 (60%) | 142 (59%) | 263 (59%) | 133 (60%) |
| • **ABC setting** | 273 (79%)* | 133 (76%)* | 110 (23%) | 40 (17%) | 171 (38%) | 85 (38%) |
| **Prior chemotherapy** | 34% received 1 prior line of chemotherapy for ABC | | No prior chemotherapy allowed in the advanced setting | | No prior chemotherapy allowed in the advanced setting | |
| **Postmenopausal at study entry - no. (%)** | 275 (79.3%) | 138 (79.3%) | 484 (100%) | 242 (100%) | 371 (83.2%) | 1810 (80.7) |
| **Visceral metastasis – no. (%)** | 206 (59.4%) | 105 (60.3%) | 293 (60.5%) | 146 (60.3%) | 245 (54.9%) | 128 (57.4%) |

1. Cristofanilli M et al. *Lancet Oncol* 2016;17:425–39. 2. Slamon D et al. *J Clin Oncol* 2018;36:1–8; 3. Sledge GW et al. *J Clin Oncol* 2017;35:2875–2884.

# Prognosis of metastatic breast cancer




- Patients with de novo metastatic breast cancer have a better prognosis
- Patients with MFI >24 months have a better prognosis

Lobbezoo DJ et al. B J Cancer 2015; Shen T et al. Hum Pathol 2017

# Ongoing Adjuvant Trials With CDK4/6 Inhibitors

| | PENELOPE-B | PALLAS | MonarchE | NATALEE |
|---|---|---|---|---|
| **Sponsor/Collaborator** | GBG | ABCSG/AFT | Eli Lilly/NSABP | Novartis/TRIO |
| **CDK 4/6 Inhibitor** | Palbociclib | Palbociclib | Abemaciclib | Ribociclib |
| **Sample Size** | 1250 | 5600 | 4430 | 4000 |
| **Design** | Phase 3 randomized placebo-controlled | Phase 3 randomized open label | Phase 3 randomized open label | Phase 3 (non) randomized open label |
| **Patient population** | High-risk | Stage II-III | High-risk | Stage II-III |
| **Duration of Combination Therapy** | 1 year (13 cycles) | 2 years (26 cycles) In at least 5 years ET total | 2 years (26 cycles) In at least 5 years ET total | 3 years |
| **Primary Endpoint** | iDFS | iDFS | iDFS | iDFS |
| **Estimated Primary Completion Date** | December 2020 | September 2020 | April 2021 | December 2025 |

# Summary and Conclusion

- CDK4/6 inhibitors improve PFS in 1st and 2nd line mBC which translates into an Overall Survival improvement – **what more do we want!**
- Outcome improves irrespective of pretreatment, menopausal status endocrine sensitivity and site of metastases
- So far no biomarkers identified to selec a subgroup for more or less benefit
- Trials cannot and should not be compared
  - Different population
  - Different subgroup definitions
- **Combine all CDK4/6 clincal trial data (in 1st and 2nd line) and perform a meta-analysis to reveal any potential differences in subgroups**

# ESMO BREAST CANCER

Annual Congress

## BERLIN GERMANY
## 7-9 MAY 2020

The ESMO Breast Cancer, a multidisciplinary global meeting held in Europe, involving the top worldwide recognised experts, is the complete platform for all Breast Cancer researchers and clinicians with a specific interest in innovation, translational oncology and care.


ESMO

esmo.org