

Carcinoma mammario HR+/HER2-negativo

Novità sul trattamento della malattia avanzata

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Convegno regionale Aiom Sicilia
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Addressing Issues With Endocrine Therapy in Metastatic Disease

- Historically, ET is the first targeted treatment approach in breast cancer which targets estrogen synthesis and its receptors
- Today, a new generation of targeted treatments are available which target ER pathways in combination with ET to try to overcome endocrine treatment resistance
- However, in the ER-positive, HER2-negative, endocrine-resistance patient population, chemotherapy is still an important and valid option



Guideline Recommendations for ER-Positive/HER2-Negative MBC

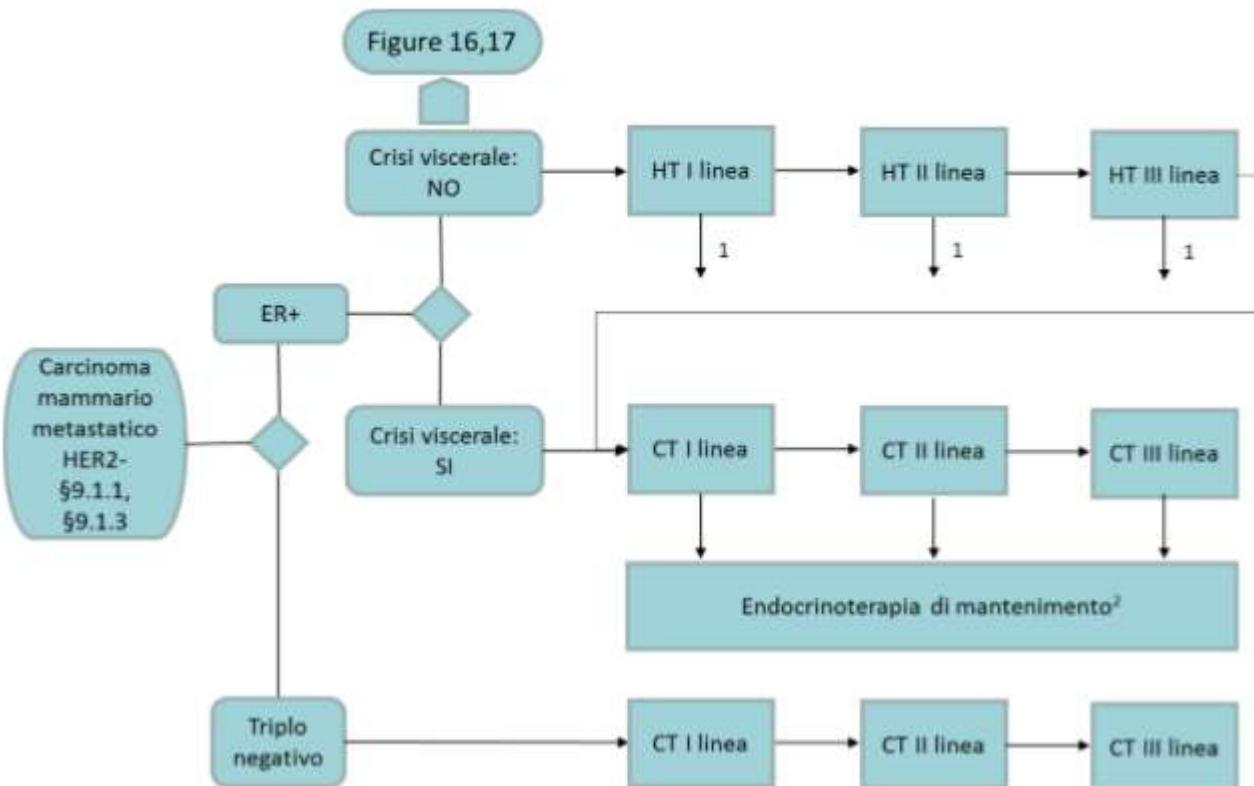
- In patient with visceral crisis and clear arguments for primary endocrine resistance, ET is the preferred option^[a-c]
- Several options are possible in first-line MBC according to previous treatment exposure and "estimation" of endocrine sensitivity and patient parameters^[a-c]
 - Among these options are CDK4/6 inhibitors which are showing promise and are continuing to become clinically useful in everyday practice

a. Rugo H, et al. *J Clin Oncol*. 2016;34:3069-3103.

b. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Breast Cancer. V2.2017.

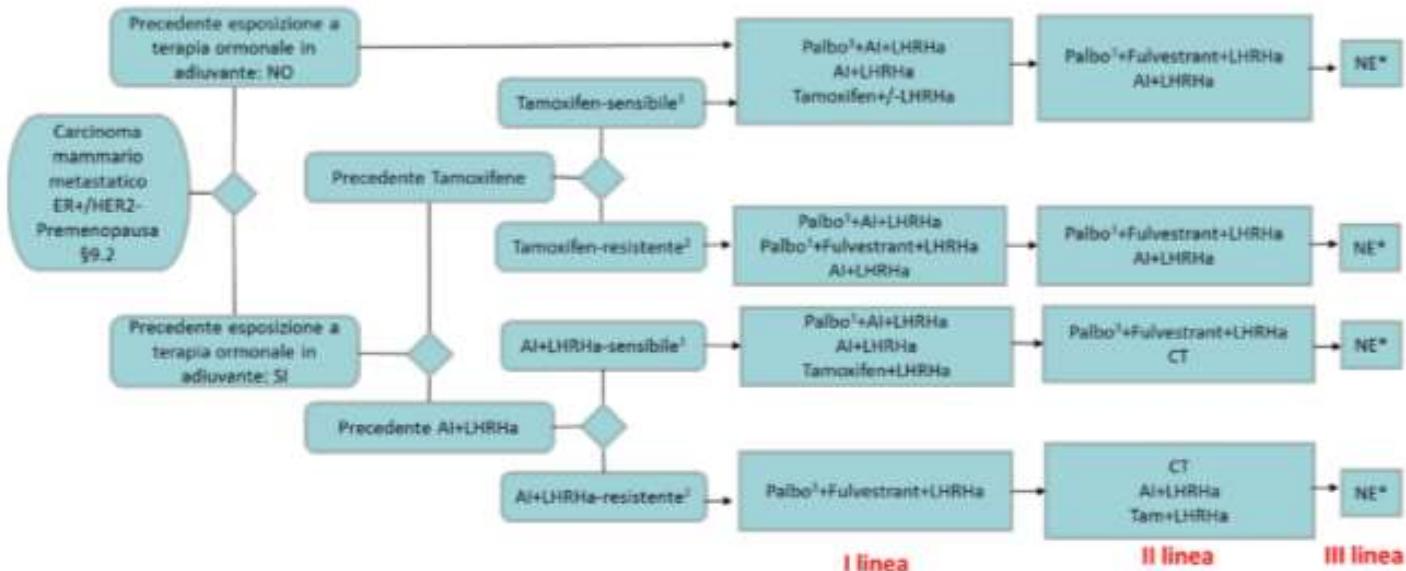
c. Cardoso F, et al. *Annals of Oncology*. 2017;28:16-33.

CARCINOMA MAMMARIO METASTATICO HER2- NEGATIVO



LINEE GUIDA
2018

CARCINOMA MAMMARIO METASTATICO ER+/HER2- NEGATIVO: Terapia ormonale in premenopausa



Nota 1- intervallo tra la fine del trattamento adiuvante e la comparsa di metastasi > 12 mesi

Nota 2- comparsa di metastasi durante il trattamento adiuvante oppure entro 12 mesi dalla fine del trattamento adiuvante

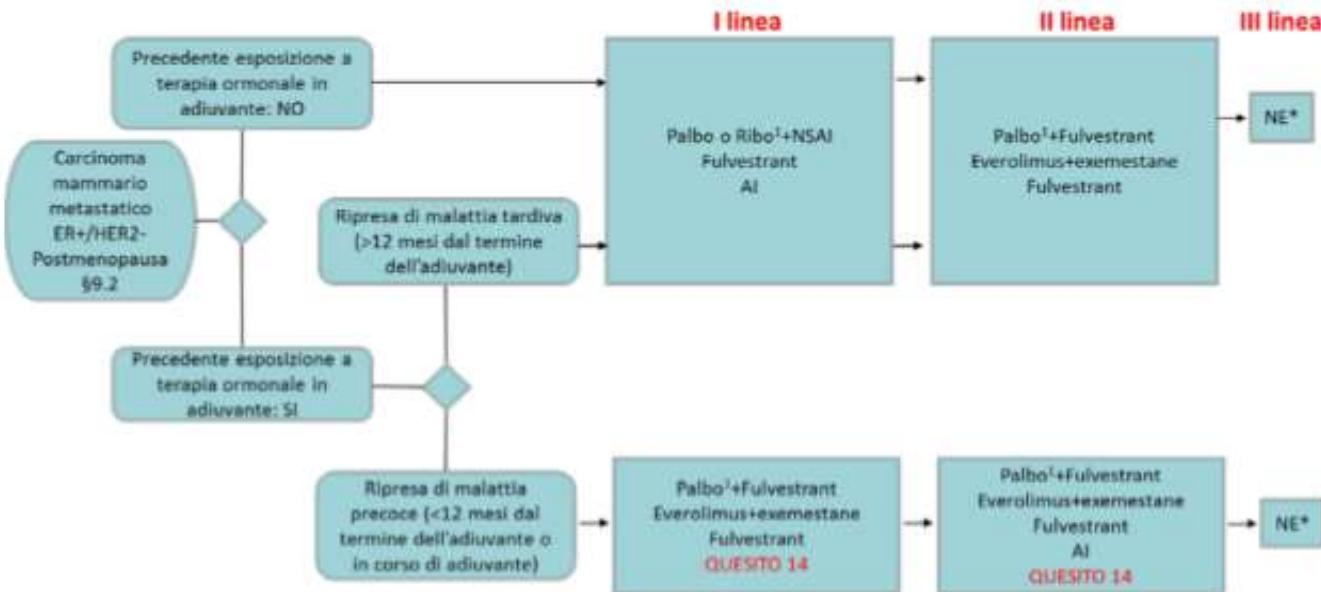
Nota 3- Palbociclib è indicato per il trattamento del carcinoma mammario localmente avanzato o metastatico HR-positivo e HER2-negativo: in associazione ad un inibitore dell'aromatasi; in associazione a fulvestrant in donne che hanno ricevuto una terapia endocrina precedente. In donne in pre - o perimenopausa, la terapia endocrina deve essere associata ad un agonista dell'ormone di rilascio dell'ormone luteinizzante (LHRH).

NE*: non vi sono evidenze disponibili che indichino uno specifico trattamento. La scelta dipende dai farmaci non ancora ricevuti in precedenza o dall'opportunità o meno di proseguire la terapia ormonale

Legenda: LHRHa = Luteinizing hormone-release hormone; AI = aromatase inhibitor;

La scelta del trattamento in II linea dipende dai farmaci già ricevuti.

CARCINOMA MAMMARIO METASTATICO ER+/HER2- NEGATIVO: Terapia ormonale in post-menopausa



Nota 1- Attualmente Palbociclib e Ribociclib sono approvati e rimborsati in Italia. Palbociclib è indicato per il trattamento del carcinoma mammario localmente avanzato o metastatico HR-positivo e HER2-negativo in associazione ad un inibitore dell'aromatasi; in associazione a fulvestrant in donne che hanno ricevuto una terapia endocrina precedente. In donne in pre - o perimenopausa, la terapia endocrina deve essere associata ad un agonista dell'ormone di rilascio dell'ormone luteinizzante (LHRH). Ribociclib è indicato in combinazione con un inibitore dell'aromatasi come terapia iniziale a base endocrina per il trattamento delle donne in post-menopausa con carcinoma mammario in stadio localmente avanzato o metastatico HR-positivo e HER2-negativo.

NE*: non vi sono evidenze disponibili che indichino uno specifico trattamento. La scelta dipende dai farmaci non ancora ricevuti in precedenza o dall'opportunità o meno di proseguire la terapia ormonale

Legenda: NSAI = inibitore dell'aromatasi non steroideo; AI= inibitore dell'aromatasi

SYSTEMIC THERAPY FOR ER AND/OR PR-POSITIVE RECURRENT OR STAGE IV (M1) DISEASE**HER2-Negative and Premenopausal**[See Systemic Treatment of Stage IV \(M1\) Disease \(BINV-21\)](#)**HER2-Negative and Postmenopausal****Preferred regimens:**

- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Selective ER down-regulator (fulvestrant, category 1)¹
- Tamoxifen or toremifene
- Steroidal aromatase inactivator (exemestane)
- CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) + aromatase inhibitor (category 1)^{2,3}
- CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) + fulvestrant (category 1)^{2,3}
- Exemestane + everolimus^{2,4}
- Fulvestrant + everolimus
- Tamoxifen + everolimus

Useful in certain circumstances:

- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol
- Ribociclib + tamoxifen (category 1)⁵
- Abemaciclib^{2,6}

HER2-Positive and Premenopausal[See Systemic Treatment of Stage IV \(M1\) Disease \(BINV-23\)](#)**HER2-Positive and Postmenopausal**

- Aromatase inhibitor ± trastuzumab
- Aromatase inhibitor ± lapatinib
- Aromatase inhibitor ± lapatinib + trastuzumab
- Fulvestrant ± trastuzumab
- Tamoxifen ± trastuzumab

¹A single study (S0226) in women with hormone receptor-positive breast cancer and no prior chemotherapy, biological therapy, or endocrine therapy for metastatic disease demonstrated that the addition of fulvestrant to anastrozole resulted in prolongation of time to progression. Subset analysis suggested that patients without prior adjuvant tamoxifen and more than 10 years since diagnosis experienced the greatest benefit. Two studies with similar design (FACT and SOFEA) demonstrated no advantage in time to progression with the addition of fulvestrant to anastrozole.

²If there is disease progression while on CDK4/6 inhibitor therapy, there are no data to support an additional line of therapy with another CDK4/6-containing regimen. Likewise, if there is disease progression while on a everolimus-containing regimen, there are no data to support an additional line of therapy with another everolimus regimen.

³CDK4/6 inhibitor in combination with an aromatase inhibitor (anastrozole, letrozole, or exemestane) or fulvestrant may be considered as a treatment option for first-line therapy for women who are postmenopausal or premenopausal (receiving ovarian suppression or ablation with an LHRH agonist) with hormone-receptor positive, HER2-negative metastatic breast cancer. Fulvestrant has been combined with CDK4/6 inhibitors (palbociclib, ribociclib) in the first-line setting in two randomized trials.

⁴A combination of exemestane with everolimus can be considered for patients who meet the eligibility criteria for BOLERO-2 (progressed within 12 mo or on non-steroidal AI).

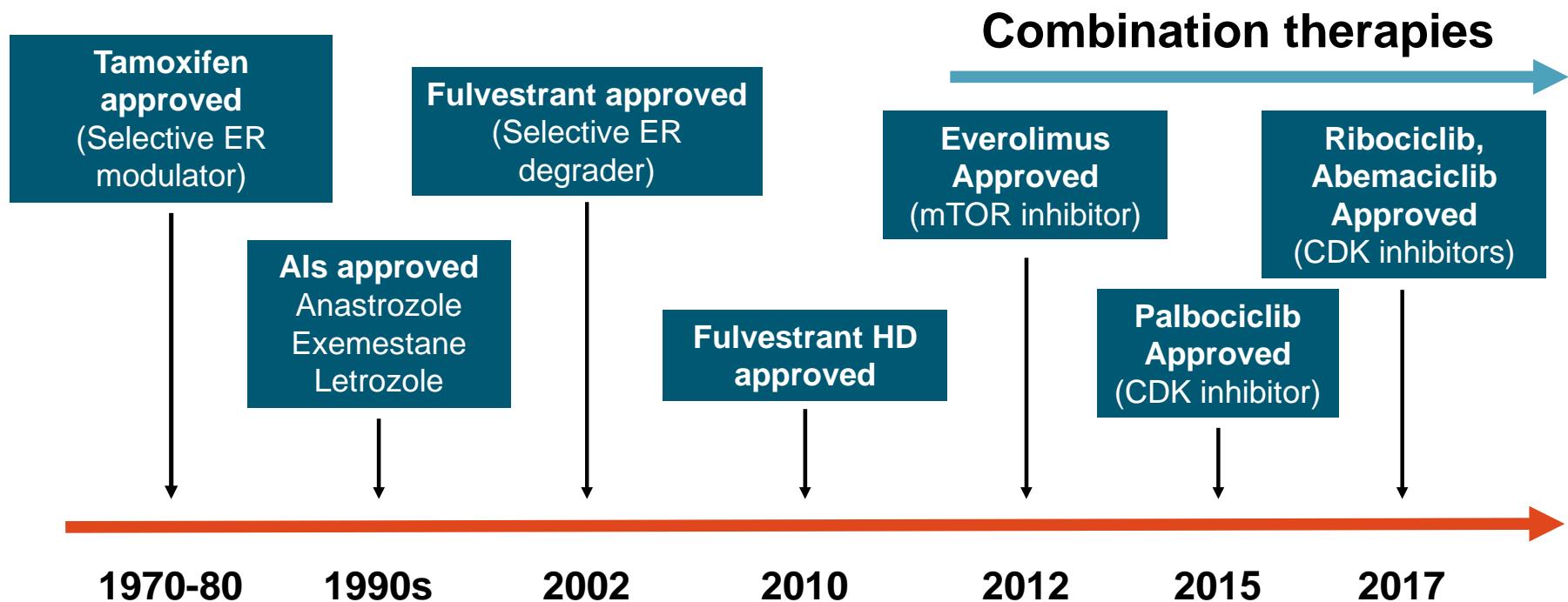
⁵Ribociclib + tamoxifen is not considered a preferred first-line therapy due to QTc prolongation risk but may be considered in certain circumstances as a treatment option for first-line therapy with ovarian suppression or ablation for premenopausal patients with hormone-receptor positive, HER2-negative metastatic breast cancer.

⁶Indicated after progression on prior endocrine therapy and prior chemotherapy in the metastatic setting.

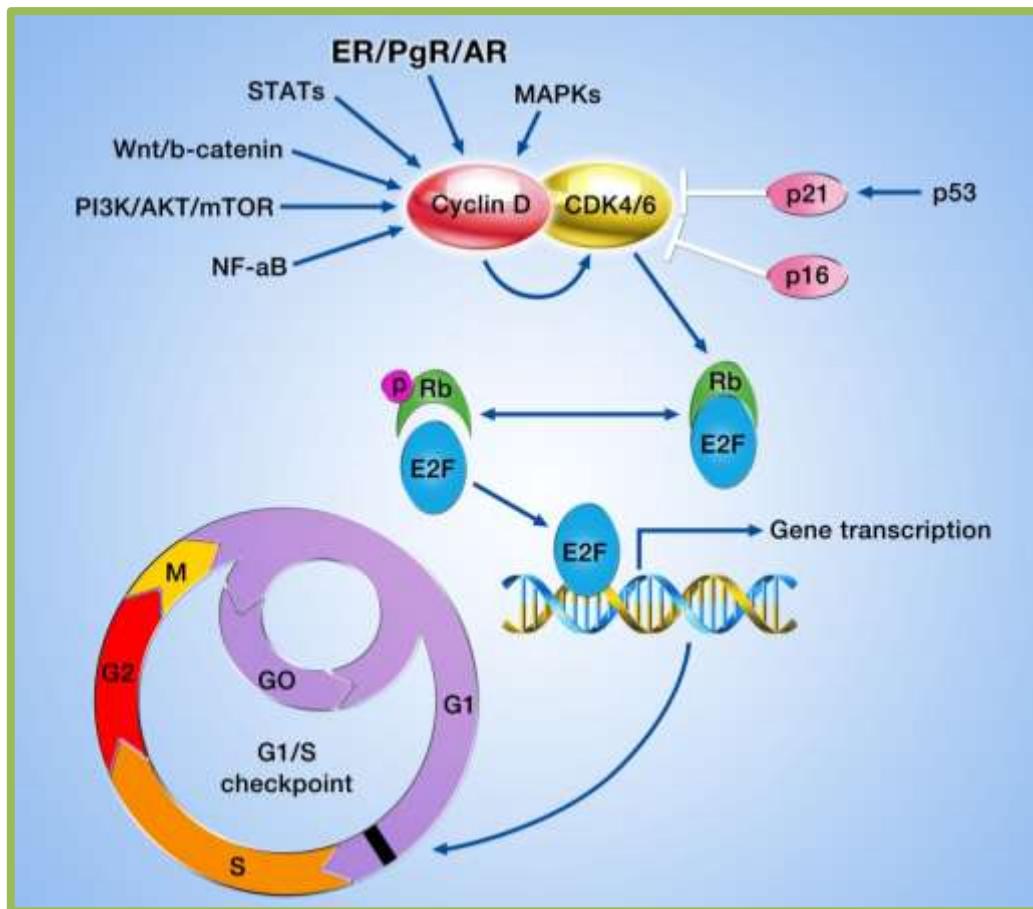
Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Changing Landscape of HR+/HER2- MBC



The Cyclin D–CDK4/6–INK4–Rb Pathway Regulates Cell Cycle Progression



- CDK4/6 control cell cycle progression from G₁ to S phase by regulating the activity of Rb^{1–4}
 - E2F activates transcription of genes necessary for S-phase entry and cell cycle progression
 - Rb inhibits this transcription by binding to and sequestering E2F
 - Synthesis of D-type cyclins (cyclin D1, D2, and D3) and association with CDK4/6 is initiated in response to mitogenic signaling pathways
 - Active cyclin D–CDK4/6 phosphorylates Rb, decoupling Rb from E2F and allowing transcription of genes required for cell cycle progression
 - Cyclin D–CDK4/6 activity is inhibited by INK4 (p16^{INK4A}, p15^{INK4B}, p18^{INK4C}, p19^{INK4D}), Cip (p21^{Cip1}), and Kip (p27^{Kip1}, p57^{Kip2}) proteins

Cdk4/6 inhibitors

- I. Palbociclib
- II. Ribociclib
- III. Abemaciclib

Consistent Clinical Benefit Seen Across PALOMA Studies

PALOMA-1^[a]

Design:

- Phase 2
- Open label

Endocrine partner:

- Letrozole

Patients on study:

- n = 165

Primary endpoint: PFS

- Hazard ratio: 0.49
- Median PFS, months: 20.2 vs 10.2

Secondary endpoints, %

- Objective response rate (ITT, measurable disease): 43 vs 33, 55 vs 39
- CBR (ITT): 81 vs 58

PALOMA-2^[b]

Design:

- Phase 3
- Placebo control

Endocrine partner:

- Letrozole

Patients on study:

- n = 666

Primary endpoint: PFS

- Hazard ratio: 0.58
- Median PFS, months: 24.8 vs 14.5

Secondary endpoints, %

- Objective response rate (ITT, measurable disease): 42 vs 35, 55 vs 44
- CBR (ITT): 85 vs 70

PALOMA-3^[c]

Design:

- Phase 3
- Placebo control

Endocrine partner:

- Fulvestrant

Patients on study:

- n = 521

Primary endpoint: PFS

- Hazard ratio: 0.46
- Median PFS, months: 9.6 vs 4.6

Secondary endpoints, %

- Objective response rate (ITT, measurable disease): 19 vs 9, 25 vs 11
- CBR (ITT): 67 vs 40

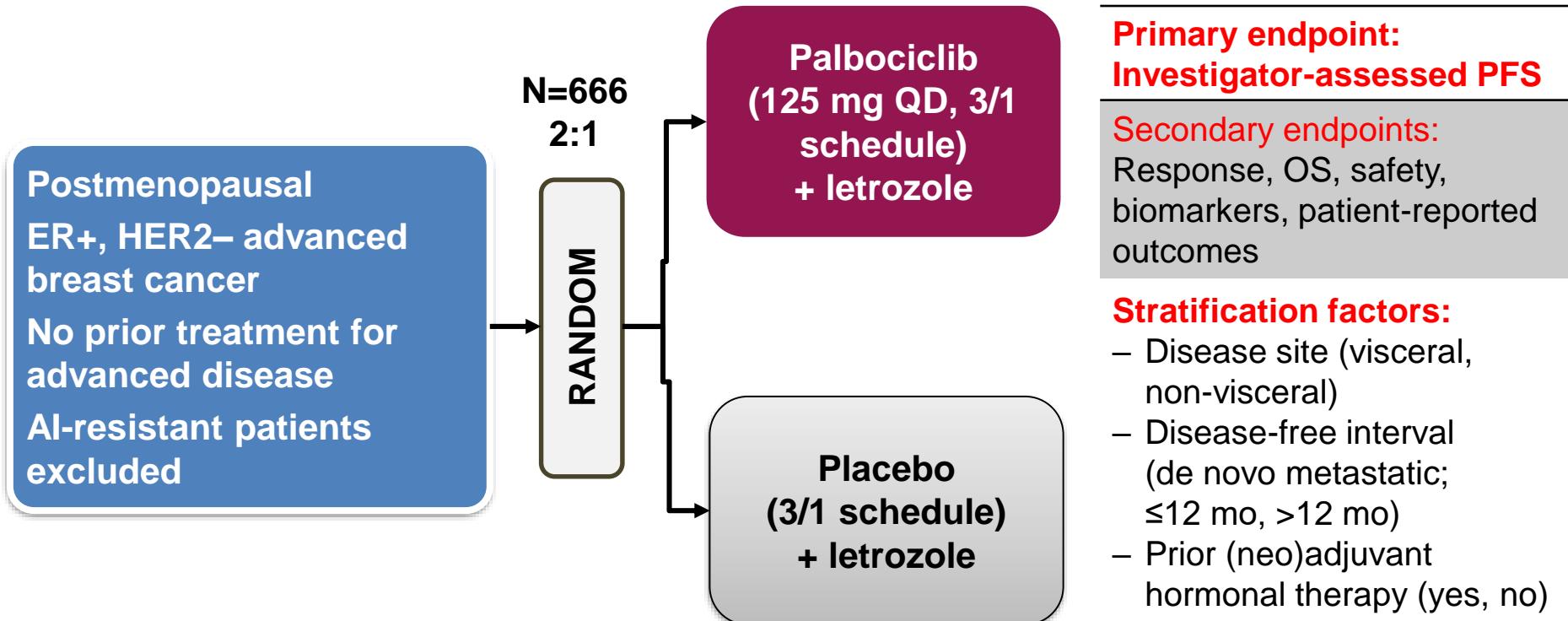
a. Finn RS, et al. *Breast Cancer Res.* 2016;18:67.

b. Finn R, et al. *N Engl J Med.* 2016;375:1925-1936.

c. Cristofanilli M, et al. *Lancet Oncol.* 2016;17:425-439.

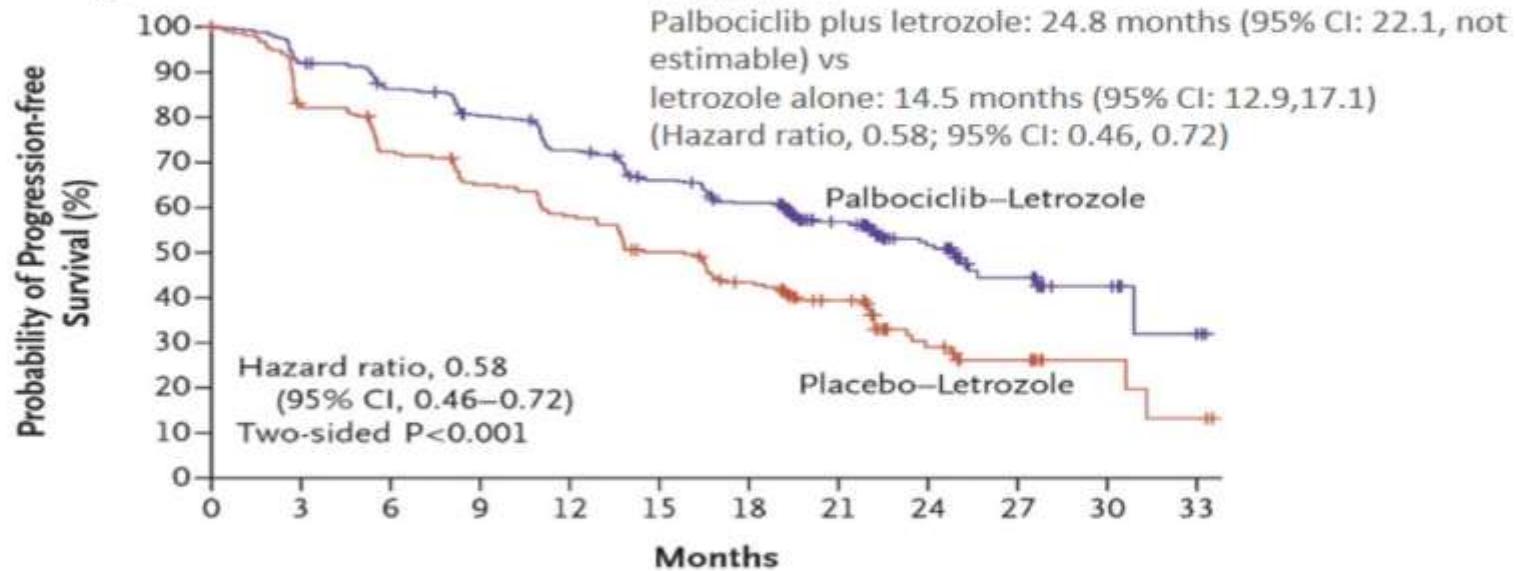
PALOMA-2

Phase III study design



First-Line PALOMA-2 Trial*: PFS Results

A Investigator Assessment



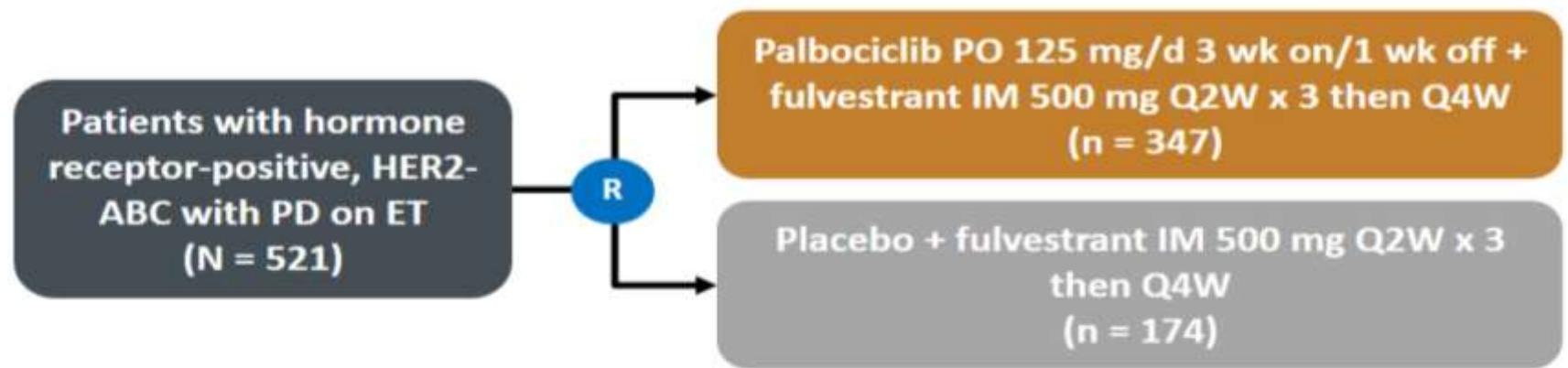
No. at Risk

Palbociclib–Letrozole	444	395	360	328	295	263	238	154	69	29	10	2
Placebo–Letrozole	222	171	148	131	116	98	81	54	22	12	4	2

*Postmenopausal women with ER-positive, HER2-negative breast cancer, who had not had prior treatment for advanced disease.

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

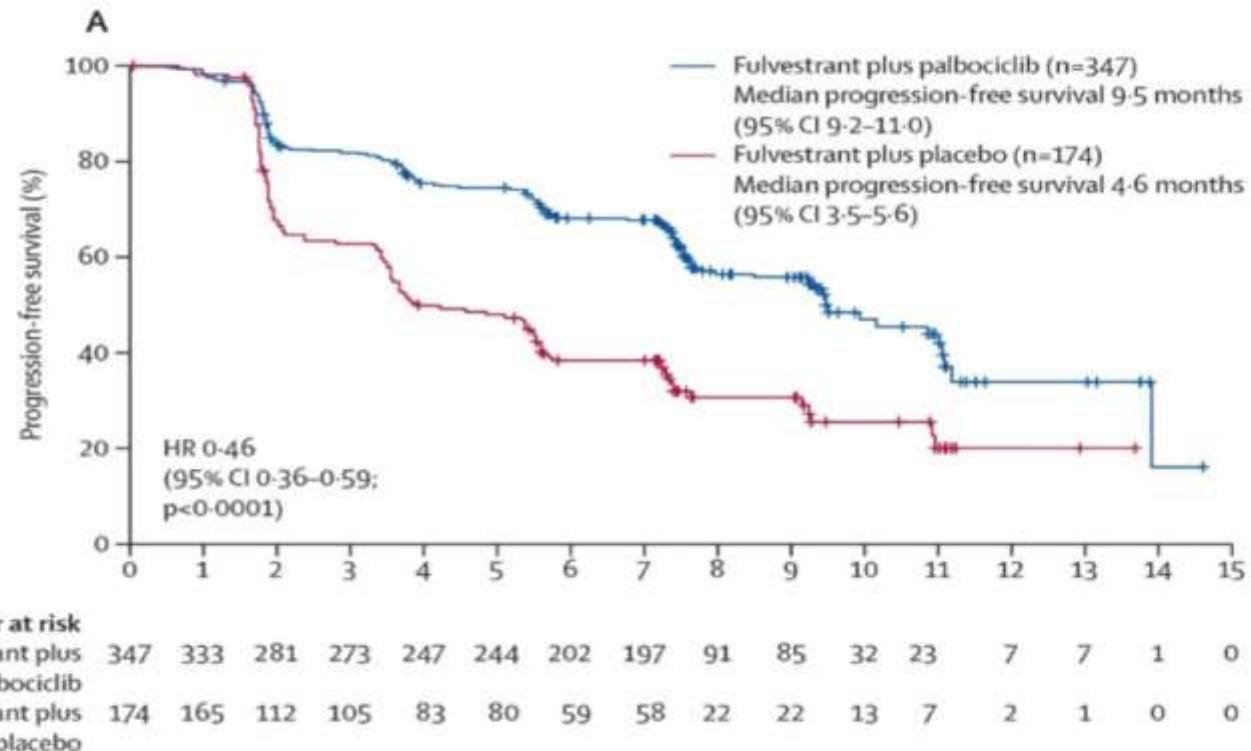
Paloma 3 trial: Palbociclib plus fulvestrant in previously treated MBC



Palbociclib + Fulvestrant	Placebo + Fulvestrant	Hazard ratio (95% CI)	P Value
Median PFS, mo	9.2	3.8	0.42 (0.32, 0.56) < .001

- Randomized, double-blind, phase 3 trial
- Most common grade 3/4 AEs with palbociclib plus fulvestrant:
 - Neutropenia, leukopenia, anemia, thrombocytopenia, fatigue

Second-Line PALOMA-3 Trial*: PFS



*HR-positive, HER2-negative MBC that had progressed on previous endocrine therapy
 Cristofanilli M, et al. *Lancet Oncol.* 2016;17:425-439.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer

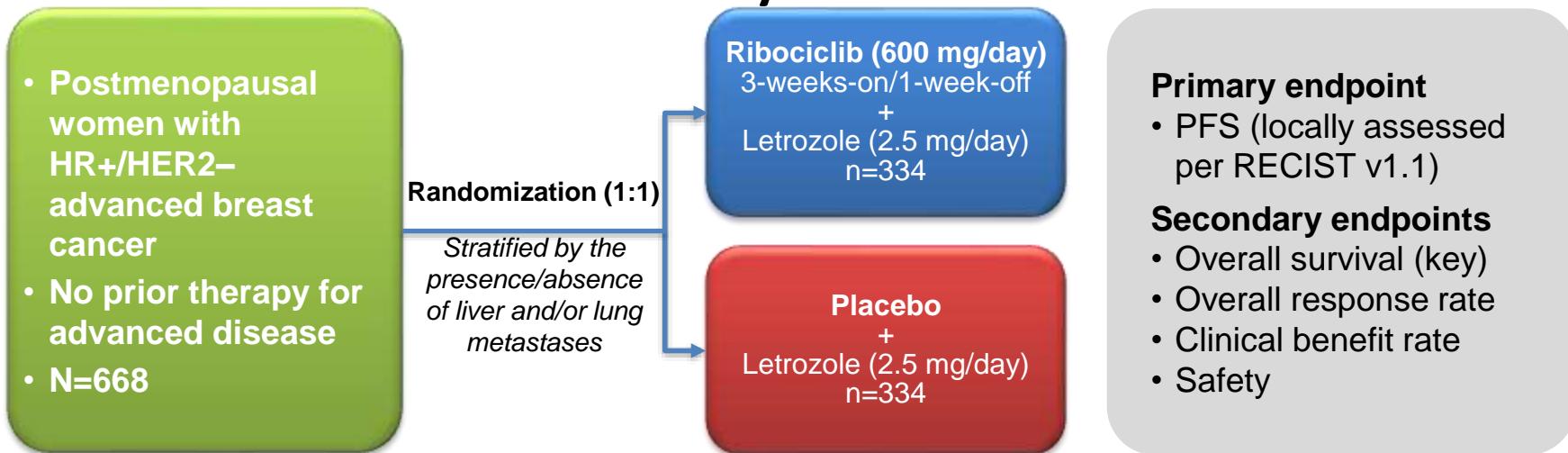
G.N. Hortobagyi, S.M. Stemmer, H.A. Burris, Y.-S. Yap, G.S. Sonke,
S. Paluch-Shimon, M. Campone, K.L. Blackwell, F. André, E.P. Winer, W. Janni,
S. Verma, P. Conte, C.L. Arteaga, D.A. Cameron, K. Petrakova, L.L. Hart,
C. Villanueva, A. Chan, E. Jakobsen, A. Nusch, O. Burdaeva, E.-M. Grischke,
E. Alba, E. Wist, N. Marschner, A.M. Favret, D. Yardley, T. Bachelot, L.-M. Tseng,
S. Blau, F. Xuan, F. Souami, M. Miller, C. Germa, S. Hirawat, and J. O'Shaughnessy

<http://www.nejm.org/doi/pdf/10.1056/NEJMoa1609709>

DOI: 10.1056/NEJMoa1609709

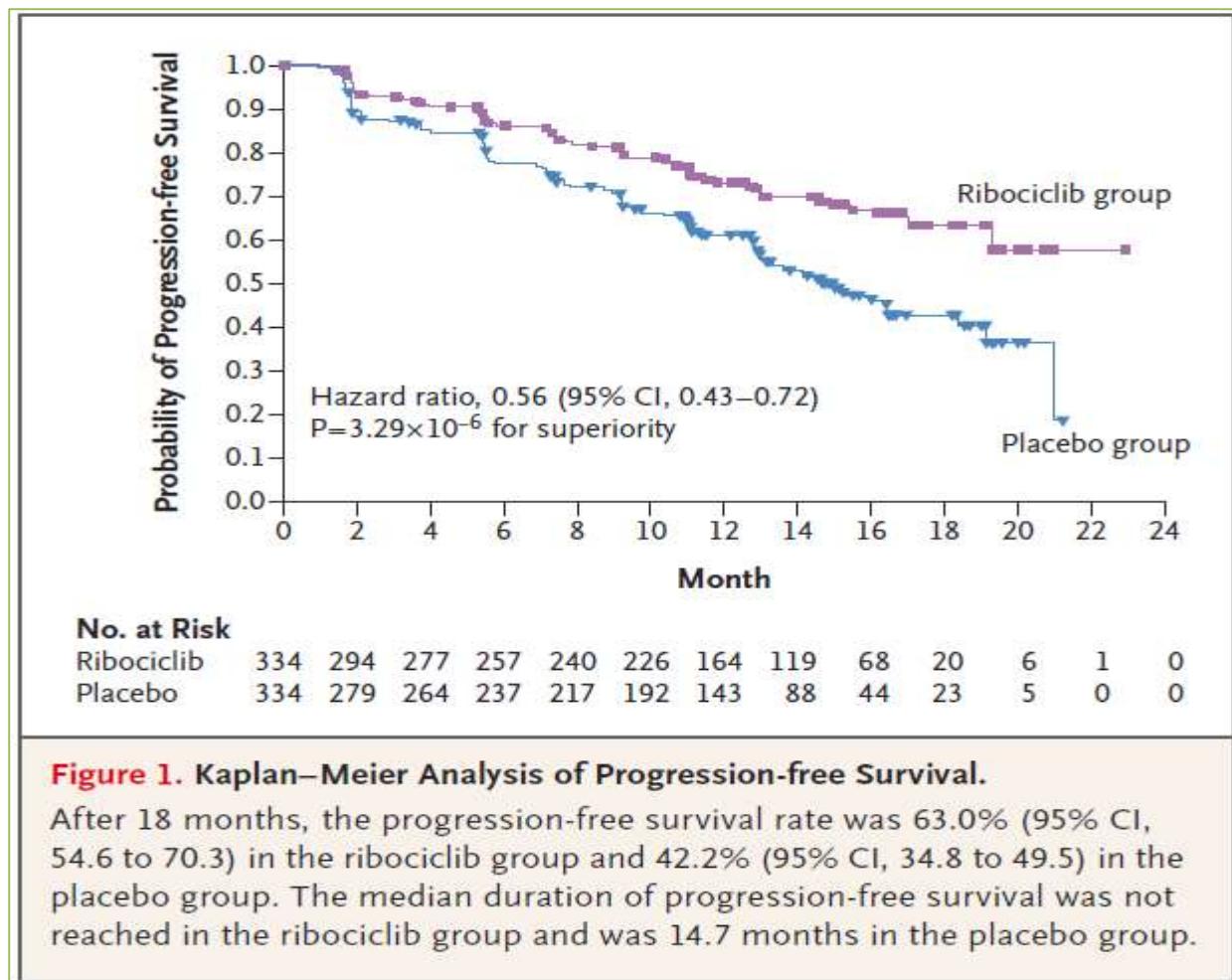
MONALEESA-2

A Phase III, Double-blind, Placebo-controlled Study of Ribociclib + Letrozole

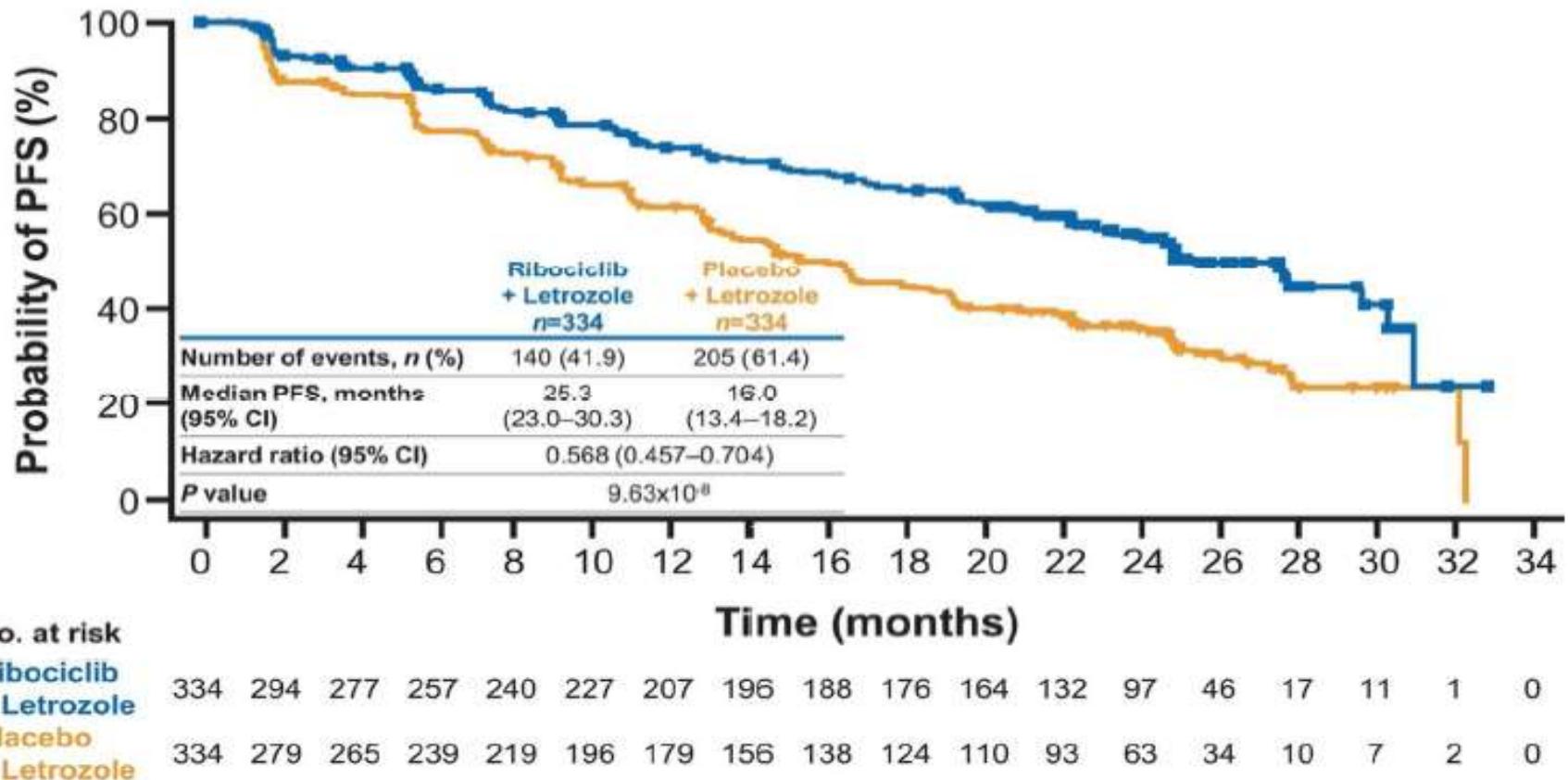


- Tumor assessments were performed every 8 weeks for 18 months, then every 12 weeks thereafter
- Final analysis planned after 302 PFS events
 - ✓ 93.5% power to detect a 33% risk reduction (hazard ratio 0.67) with one-sided $\alpha=2.5\%$
- Interim analysis planned after ~70% PFS events
 - ✓ Two-look Haybittle–Peto stopping criteria: hazard ratio ≤ 0.56 and $p < 0.0000129$

Progression free survival (from NEJM)



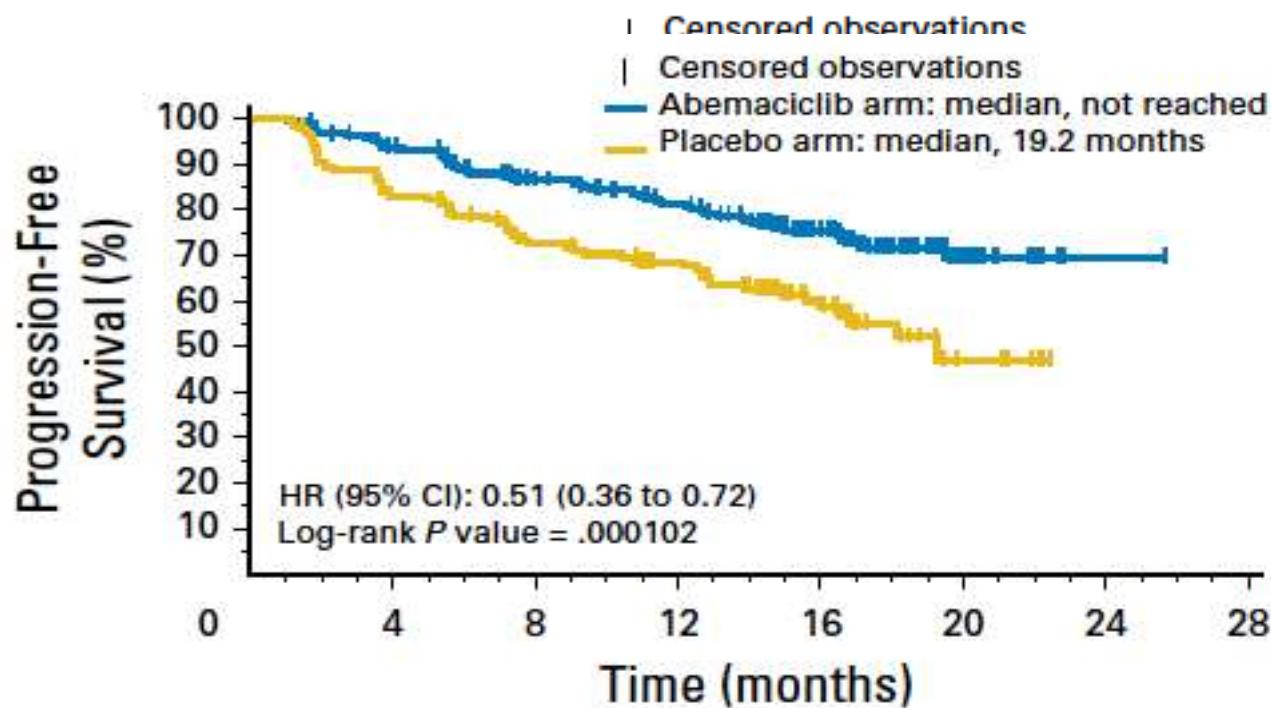
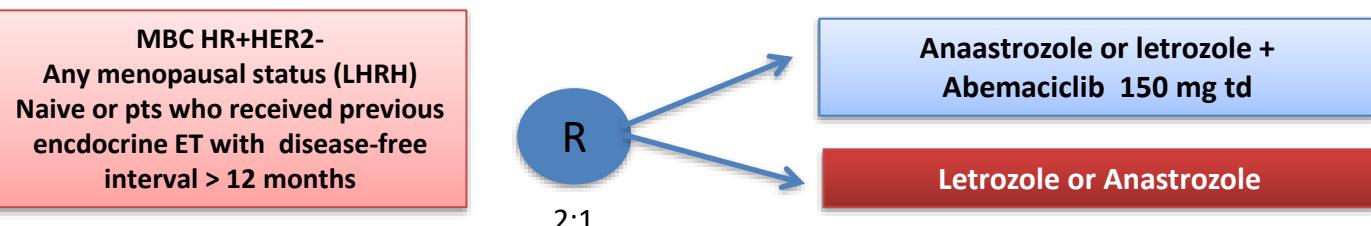
MONALEESA-2: PFS updated



MONARCH-3

Results

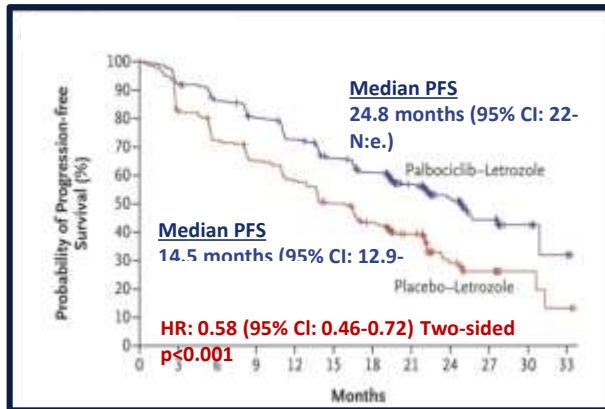
MONARCH 3²



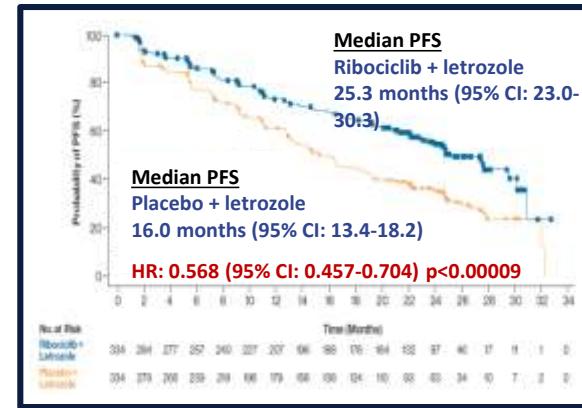
First-line Phase III CDK4/6 inhibitors: PFS

Monaleesa-2³

PALOMA-2¹

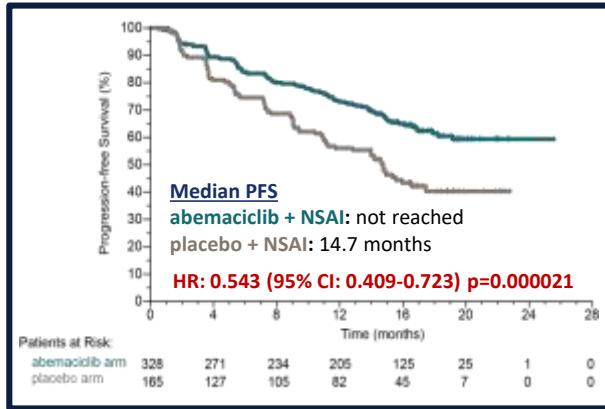


Finn RS et al. N Engl J Med
2016



Hortobagyi G, et al. Ann Oncol
2018

Monarch-3²



Goetz M et al. J Clin Oncol
2017

The final MONARCH-3 PFS data were presented at AACR 2018⁴

Abemaciclib + NSAI significantly extended median PFS vs placebo + NSAI

- 28.2 vs. 14.8 months, respectively
HR, 0.54; 95% CI, 0.418-0.698; $p = 0.000002$

First-line PFS outcome data are not directly comparable between the different Phase III studies

95% CI, 95% confidence interval; CDK, cyclin-dependent kinase; HR, hazard ratio; N:e, not evaluable; NSAI, non-steroidal aromatase inhibitor; ORR, objective response rate; PFS, progression-free survival.
1. Finn RS, Martin M, Rugo HS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med 2016;375(20):1925-36. 2. Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib as Initial Therapy for Advanced Breast Cancer. J Clin Oncol 2017;35(32):3638-46. 3. Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. Ann Oncol 2018 Apr 27. doi: 10.1093/annonc/mdy155. [Epub ahead of print]. 4. Goetz M, Martin M, Di Leo A, et al. Abstract CT040: MONARCH 3: Abemaciclib as initial therapy for patients with HR+, HER2- advanced breast cancer - Results from the preplanned final PFS analysis. AACR Annual Meeting 2018; April 14-18, 2018; Chicago, IL.

Safety/Tolerability

CDK4/6 Inhibitors: Tolerability

- Overall, CDK4/6 inhibitors are well tolerated^[a]
 - Neutropenia, leukopenia, and fatigue are the most common adverse events
 - Neutropenia is generally uncomplicated
- Each CDK4/6 inhibitor has its own safety/tolerability profile^[b-d]

a. Abraham J. *JCSO*. 2016;14:407-408.

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

c. Hortobagyi GN, et al. *N Engl J Med*. 2016;375:1738-1748.

d. Dickler MN, et al. *J Clin Oncol*. 2016;34 (suppl; abstr 510).

CDK4/6 Inhibitors: Incidence of Neutropenia

	Palbociclib ^[a]	Ribociclib ^[b]	Abemaciclib ^[c]			
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Neutropenia, %	79.5	56.1/10.4	74.3	49.7/9.6	87.7	22.3/4.6

- The incidence of febrile neutropenia is low (< 2%)^[a-c]
- Monitoring for neutropenia
 - Every 2 weeks for the first couple of cycles; less frequent as patient tolerates treatment
 - Dose adjustments may be required for grade 3/4 neutropenia

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

b. Hortobagyi GN, et al. *N Engl J Med.* 2016;375:1738-1748.

c. Dickler MN, et al. *J Clin Oncol.* 2016;34 (suppl; abstr 510).

Recommended Palbociclib Dose Adjustments for Patients With Neutropenia

Grade*	Palbociclib Dose Adjustment†
Grade 1 or 2	No dose adjustment
Grade 3 uncomplicated neutropenia	Day 1 of cycle: withhold palbociclib, repeat CBC monitoring within 1 week. When recovered to grade ≤ 2 , start the next cycle at same dose. Day 14 of first 2 cycles: continue palbociclib at current dose to complete cycle. Repeat CBC on day 21. Consider dose reduction in cases of prolonged (> 1 week) recovery from grade 3 or recurrent grade 3 neutropenia in subsequent cycles
Grade 3 neutropenia with documented infection or fever $\geq 38.5^{\circ}\text{C}$	Withhold palbociclib until recovery to grade ≤ 2 ; resume at next lower dose
Grade 4 neutropenia	Withhold palbociclib until recovery to grade ≤ 2 ; resume at next lower dose

*ANC: grade 1: ANC $<$ LLN: $1500/\text{mm}^3$; grade 2 ANC: $< 1500 \text{ mm}^3$; grade 3 ANC: $< 1000/\text{mm}^3$; grade 4 ANC $< 500/\text{mm}^3$.

†Dose levels = 125 mg/day (starting), 100 mg/day, and 75 mg/day.

European Medicines Agency. Palbociclib (Ibrance) summary of product characteristics.

The Importance of Monitoring QTc When Using CDK4/6 Inhibitors

- QTc duration depends on cardiac frequency
- The ULN for a cardiac frequency of 60 beats/min is theoretically
 - 450 msec in men; "borderline if 430 to 450 msec"
 - 470 msec in women ; "borderline if 450 to 470 msec"
- The effect of palbociclib on the QT interval corrected for heart rate (QTc) interval was evaluated using time matched ECG change from baseline and PK data^[a]
 - The upper bound of the one-sided 95% CI for the increase from baseline in QTc at all time points at steady state concentrations at the recommended dose of 125 mg was less than 8 msec;
 - Therefore, at the recommended dose, no palbociclib relevant effects on QT have been observed
- Ribociclib has been shown to prolong the QT interval in a concentration-dependent manner, with estimated mean increase in QTc interval exceeding 20 msec (22.9 msec (90% CI: 21.6, 24.1)) at the mean steady-state Cmax following administration at 600 mg once daily dose^[b]
 - Dose modification and management for QT prolongation when using ribociclib can be found in the PI

Main differences in toxicity between CDK 4 and 6 inhibitor

AEs, *% Any Gr	PALOMA-2 ^[1,2]			MONALEESA-2 ^[3]			MONARCH 3 ^[4,5]		
	Palbociclib + Letrozole (n=44)	Ribociclib + Letrozole (n=34)	Abemaciclib + NSAID (n=27)	Any Gr	Gr 2	Gr 3	Any Gr	Gr 2	Gr 3
Neutropenia	79.5	56.1	10.4	76.9	52.4	9.6	41.3	19.6	1.5
QTcF prolongation									
▪ >50ms vs BL	NR	NR	NR	3.0	--	--	NR	NR	NR
▪ ≥1 post-BL ≤80ms	NR	NR	NR	3.6	--	--	NR	NR	NR
▪ ≥1 post-BL ≤500ms	NR	NR	NR	0.6	--	--	NR	NR	NR
Gastrointestinal									
▪ Diarrhea	26.1	1.4	0	38.3	2.4	0	81.3	9.5	0
▪ Vomiting	15.5	0.5	0	33.5	3.6	0	28.4	1.2	0
▪ Abdominal pain	11.3	0.9	0	NR	NR	NR	29.1	1.2	--
▪ Decreased appetite	14.9	0.7	0	20.7	1.5	0	24.5	1.2	0
LFTs									
▪ Increased ALT	43	2	<1	NR	NR	NR	15.6	5.8	<1
▪ Increased AST	52	3	0	NR	NR	NR	15	3	0
▪ Increased ALT, AST, and/or blood bilirubin	NR	NR	NR	20.1	8.4	1.8	NR	NR	NR
Fatigue	37.4	1.8	--	41.3	2.7	0.3	40.1	1.8	--

*Any-cause AEs for PALOMA-2 and MONALEESA-2; TEAEs for MONARCH 3, except for any-cause increased ALT/AST.

Drug Interactions With CDK4/6 Inhibitors

- When making the decision to use a CDK4/6 inhibitor in combination with ET, clinical and/or biological parameters and concomitant medication need to be considered
- Differences exist between the CDK4/6 inhibitors in terms of interaction with drugs that increase QTc
- Clinicians must be aware of drug-drug interactions to avoid issues with QTc
 - Many elderly patients have different medications for hypertension, diabetes, and other problems

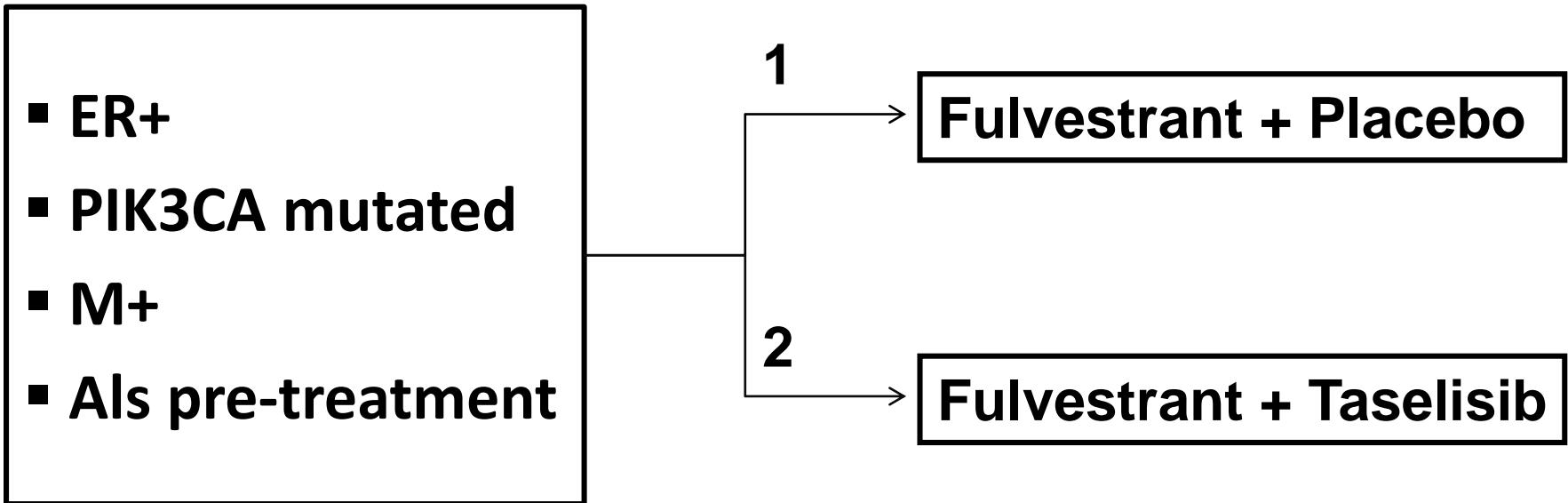


The next challenge: beyond progression to CDK 4-6 inhibitors

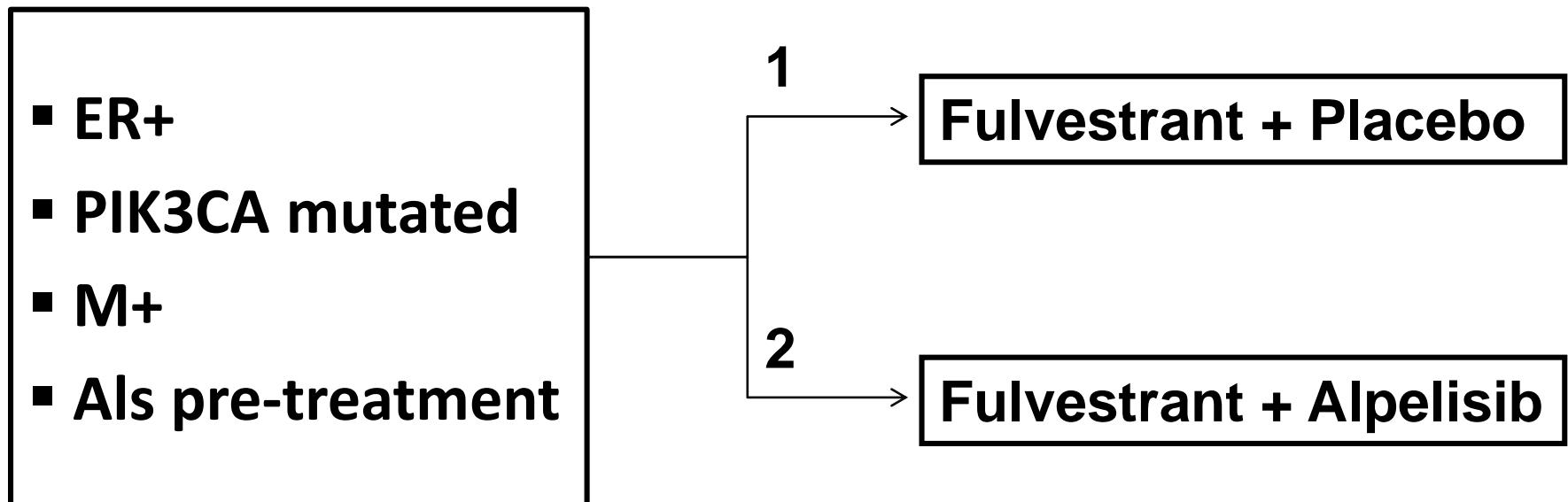
- Everolimus-exemestane
- Fulvestrant
- NSAI
- Tamoxifene
- Chemioterapia

PDK1, a PI3K-dependent protein kinase, as a potential target in the treatment of acquired resistance to CDK 4-6 inhibitors

SANDPIPER trial design



The SOLAR 1 trial design



The trial results will be presented at ESMO (October 2018) during the plenary session

GRAZIE.....