IL CARCINOMA MAMMARIO METASTATICO HR+/HER-2 –: QUALI SEQUENZE ORMONALI NEL 2018?

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MALATTIA METASTATICA

Solo il 7% circa dei tumori della mammella si presenta all'esordio come malattia metastatica

Nella maggior parte dei casi essa viene diagnosticata in pazienti con pregressa storia di neoplasia mammaria già trattata in fase neo/adiuvante.

Circa il 30% delle pazienti N-
70% di quelle N+ presenta a 10 anni una ripresa di malattia

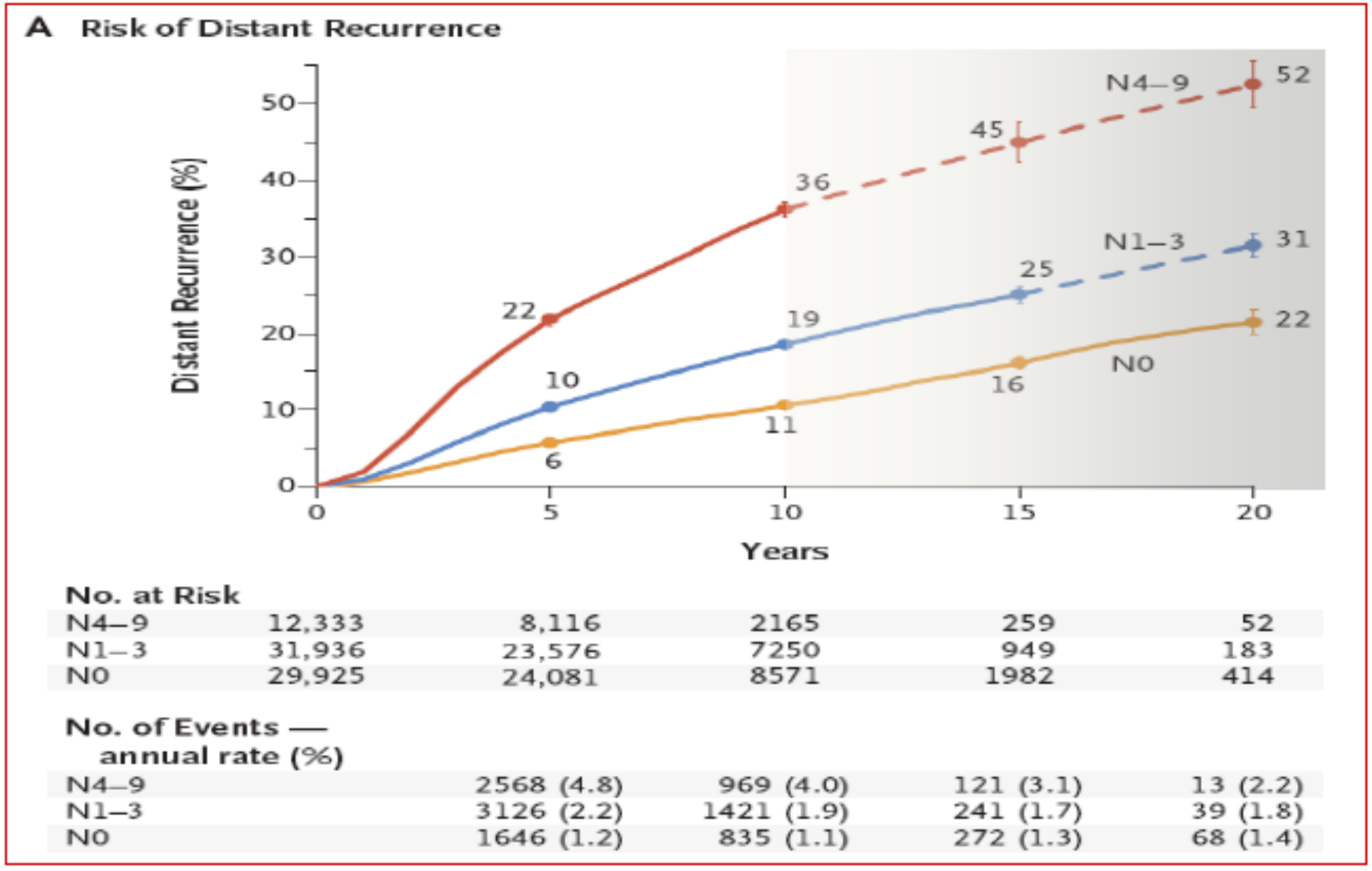
Il rischio di recidiva è differente anche in base al sottotipo biologico, che si associa anche ad una diversa preferenza per la sede di recidiva

Maggior rischio di metastasi ossee nelle neoplasie ormonosensibili

Linee guida AIOM 2017

RISCHIO DI RICADUTA NELLE PAZIENTI ER + TRATTATE CON 5 ANNI DI ORMONOTERAPIA

Circa i 2/3 delle pazienti hanno ricadute dopo un lungo periodo



No. at Risk					
N4–9	12,333	8,116	2165	259	52
N1–3	31,936	23,576	7250	949	183
N0	29,925	24,081	8571	1982	414

No. of Events — annual rate (%)				
N4–9	2568 (4.8)	969 (4.0)	121 (3.1)	13 (2.2)
N1–3	3126 (2.2)	1421 (1.9)	241 (1.7)	39 (1.8)
N0	1646 (1.2)	835 (1.1)	272 (1.3)	68 (1.4)

MALATTIA METASTATICA

Per definire i possibili obiettivi del trattamento della malattia metastatica e per la scelta del trattamento sistemico, devono essere considerate:

- **le caratteristiche cliniche e biologiche della malattia**
- **lo stato e le preferenze della paziente**

In base alle caratteristiche cliniche, la malattia metastatica può essere suddivisa in situazioni a

rischio basso (malattia indolente) ed a rischio intermedio/alto (malattia aggressiva)

Tabella 8 -Parametri utilizzabili per la definizione di malattia indolente e malattia aggressiva

CLINICHE	BIOLOGICHE[a]
Estensione della malattia (burden tumorale)	Stato di ER
Sedi di malattia (viscerali vs non viscerali) Grado di compromissione funzionale del viscere Lesioni ad elevato rischio di morte a breve termine	Stato di PgR
Intervallo libero da malattia	Stato di HER2
Precedenti trattamenti adiuvanti e/o per la malattia metastatica	Ki67[b]
Comorbidità e Performance Status	
Richieste e preferenze della paziente	

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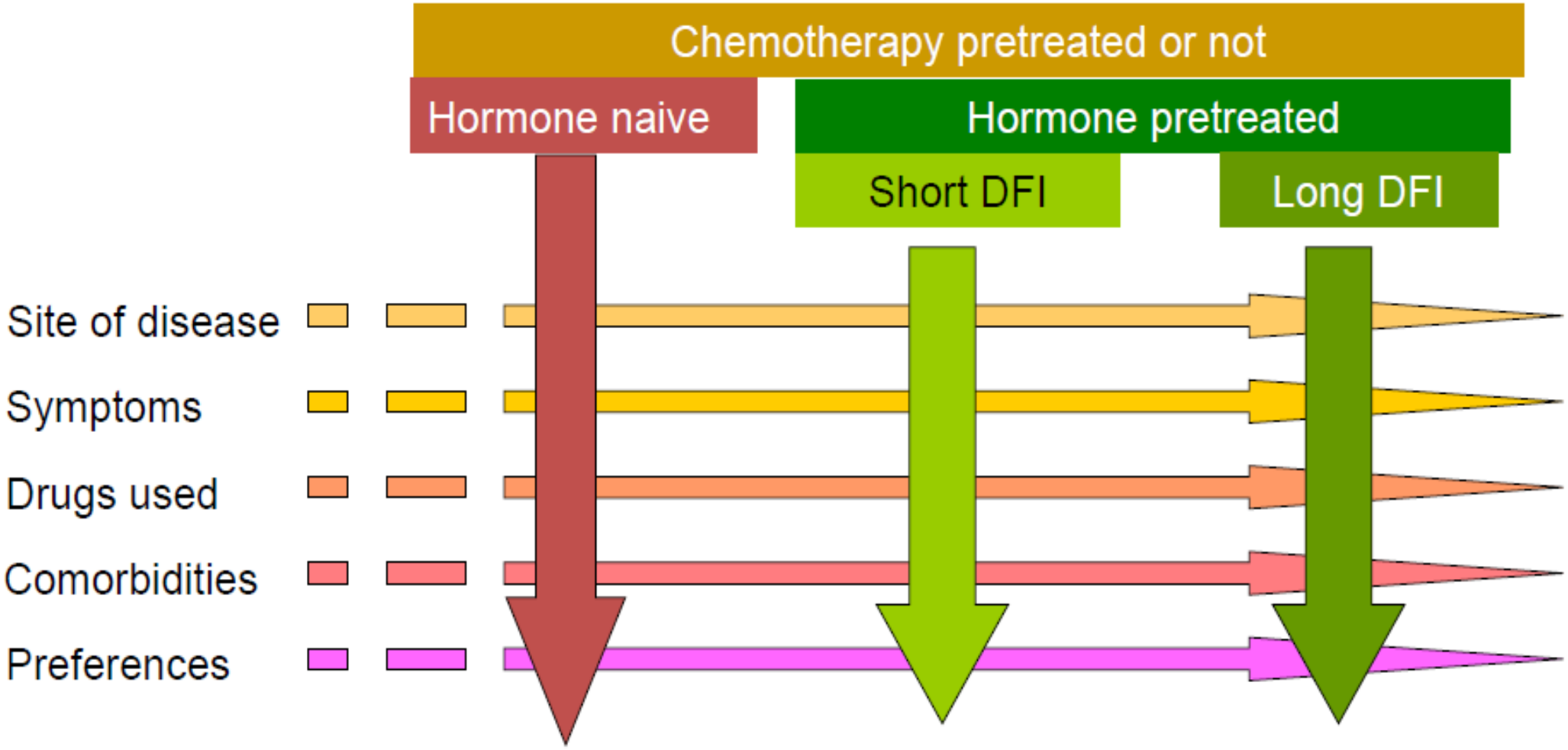
MALATTIA METASTATICA



MALATTIA METASTATICA

MALATTIA INDOLENTE **tutte le caratteristiche sottoelencate devono essere presenti:**

- **Lungo intervallo libero di malattia (> 24 mesi dal termine della terapia adiuvante)**
- **Metastasi ossee e/o ai tessuti molli;**
- **Numero limitato di lesioni metastatiche (come metastasi polmonari di piccolo volume e di numero limitato o interessamento epatico limitato e comunque inferiore al 30%**

MALATTIA AGGRESSIVA **è sufficiente una delle seguenti caratteristiche:**

- **Crisi viscerale;**
- **Presenza di elevato numero di metastasi in organi multipli**
- **Compromissione funzionale d'organo**
- **Breve intervallo libero di malattia (comparsa di metastasi durante la terapia adiuvante, o entro 12 mesi dal termine);**

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MALATTIA METASTATICA

CRISI VISCERALE

identifica uno stato di disfunzione severa di un organo (definita sulla base delle indagini di laboratorio e dei sintomi clinici) a rapida evoluzione ed a rischio di morte imminente, tale da richiedere una terapia ad effetto rapido (prevedendo che un trattamento ulteriore a progressione potrebbe non essere realizzabile). Condizioni tipiche sono rappresentate dalla linfangite polmonare diffusa, dalla insufficienza epatica o respiratoria o dalla meningosi neoplastica.

La crisi viscerale dovrebbe quindi essere distinta dai quadri di metastasi viscerali con sintomatici minori che possono essere agevolmente controllati con procedure specifiche o con terapie sintomatiche

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MALATTIA METASTATICA

OBIETTIVI DEL TRATTAMENTO

Gli obiettivi generali del trattamento della malattia metastatica sono:

- **Prolungare la sopravvivenza**
- **Ridurre o ritardare la comparsa dei sintomi**
- **Migliorare la qualità della vita**
- **Ottenere la guarigione (in casi selezionati)**

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MALATTIA METASTATICA

Indicazioni generali alla scelta del trattameto iniziale

Tumori ER+/HER2 negativi, in assenza di crisi viscerale

Ormonoterapia (OT) deve essere considerata la prima opzione di trattamento

Il trattamento ormonale dovrebbe essere proseguito (anche con linee di terapia successive) fino a quando è possibile considerare la malattia ormonosensibile

L'ormonoterapia è in grado di ottenere sopravvivenze simili a quelle ottenute con la CT, con minor numero di effetti collaterali e migliori qualità di vita

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MALATTIA METASTATICA

ORMONOSENSIBILITÁ/ORMONORESISTENZA

Non esiste una definizione condivisa dello stato di ormonosensibilità o resistenza

ORMONORESISTENZA PRIMARIA

- **Ripresa entro i primi 2 anni dall'inizio di terapia ormonale adiuvante**
- **Progressione alla terapia ormonale entro 6 mesi per la malattia metastatica.**

ORMONORESISTENZA SECONDARIA

- **Ripresa durante la terapia ormonale adiuvante, ma dopo 2 anni dall'inizio.**
- **Ripresa entro 1 anno dal termine di una terapia adiuvante ormonale.**
- **Progressione dopo almeno 6 mesi di terapia ormonale per la malattia avanzata.**

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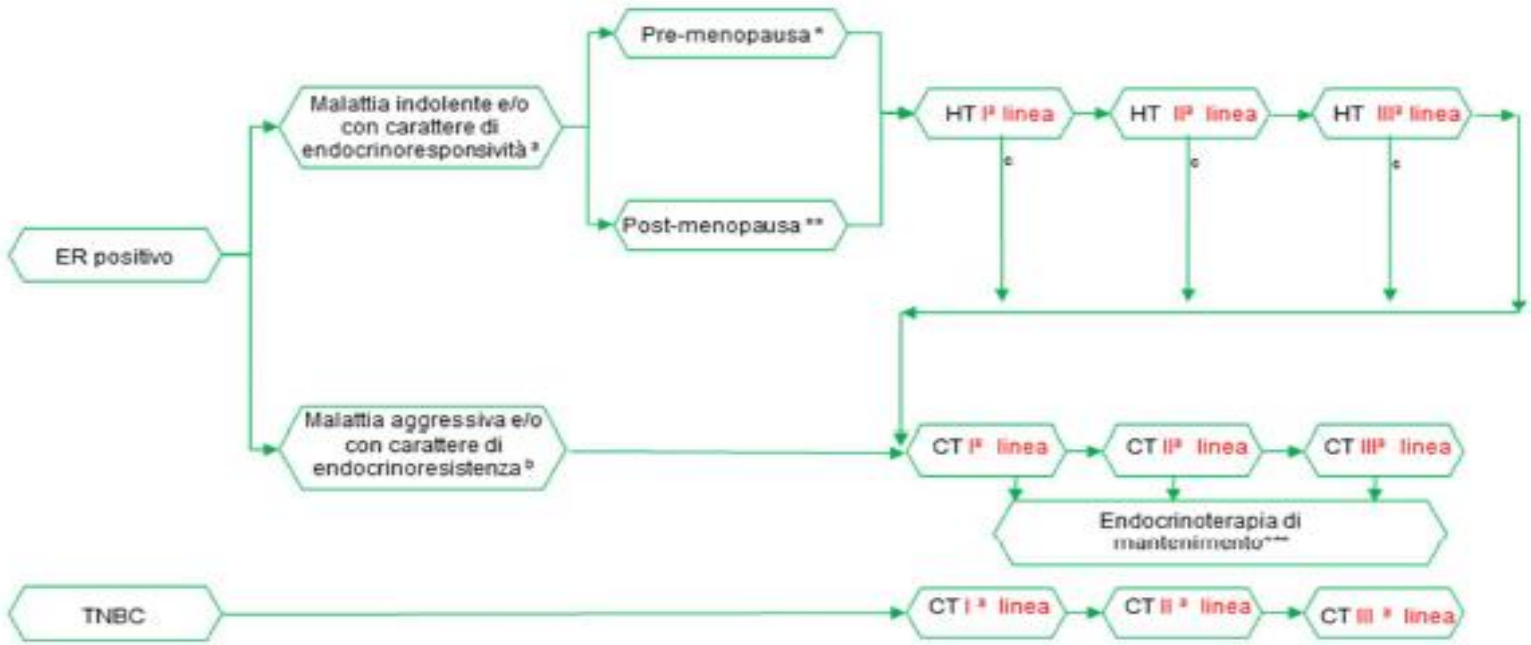
Figura 15 – CARCINOMA MAMMARIO METASTATICO ER-positivo e Triplo negativo

Terapia medica in base alle caratteristiche patologiche e cliniche (II)



Legenda: **HT**=Endocrinoterapia; **PD**=Progressione di malattia; **CT**= Chemioterapia; **ER**= Recettore Estrogenico; **TNBC**= carcinoma mammario a fenotipo triplo negativo

Nota a - Ad esempio: lungo intervallo libero tra chirurgia del tumore primitivo e metastasi, basso carico tumorale, bassa proliferazione (se disponibile valutazione Ki-67 sulla sede metastatica), elevata espressione di recettori ormonali
Nota b - Ad esempio: breve intervallo libero da malattia dopo chirurgia, crisi viscerale (con compromissione funzionale d'organo), malattia a pattern viscerale esteso, grave sintomatologia, alta proliferazione (se disponibile valutazione Ki-67 sulla sede metastatica), scarsa espressione recettoriale ormonale.
Nota c- In caso di progressione durante una linea ormonale, il passaggio ad endocrinoterapia di linea successiva o a chemioterapia va valutato caso per caso

* vedere Figura 16.
** vedere Figura 17.
*** Pur in assenza di dati da studi prospettici, l'aggiunta di un'ormonoterapia di mantenimento quando si interrompe la chemioterapia in una paziente in risposta o con malattia stabile è ammissibile

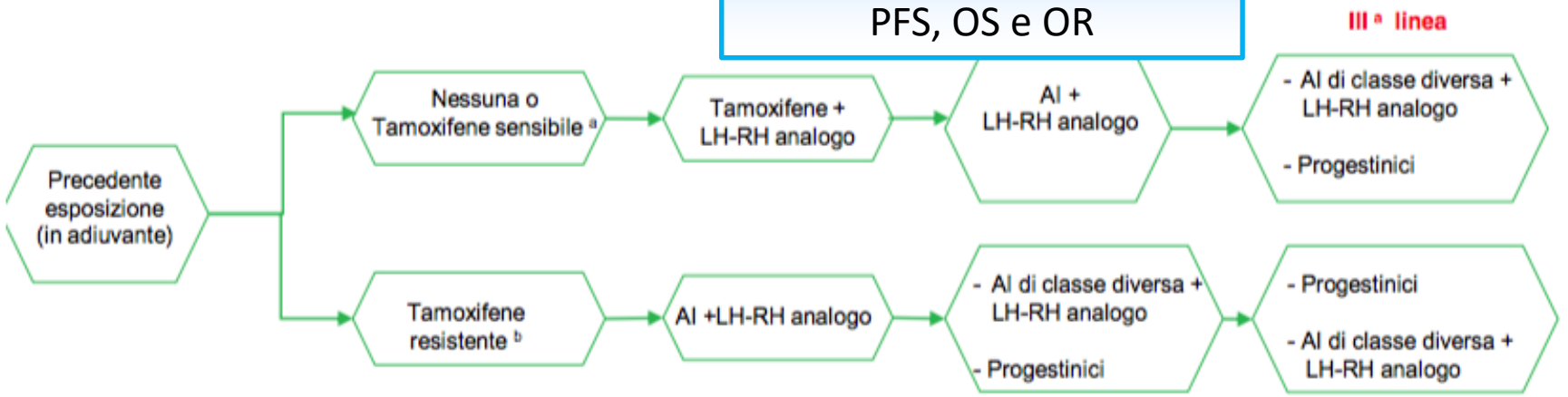
Linee guida AIOM 2017

PRE-MENOPAUSA

Figura 16 – CARCINOMA MAMMARIO METASTATICO

Terapia ormo

L'aggiunta di LHRH analogo ha mostrato vantaggi in PFS, OS e OR



L'utilizzo di FULVESTRANT +LHRH-analogo o di everolimus +IA ed LHRH-analogo, nelle pz in PD, non è al momento supportata da evidenze sperimentali

Legend … di AI:non steroideo o steroideo.

Nota a …

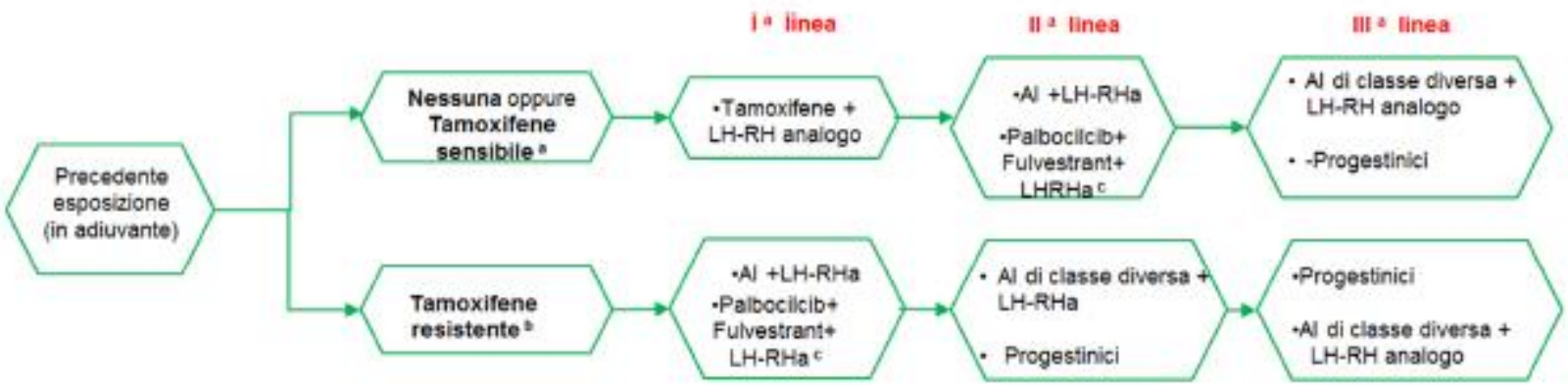
Nota b - Comparsa di metastasi durante il trattamento adiuvante oppure entro 12 mesi dalla fine del trattamento adiuvante con tamoxifene.

Linee guida AIOM 2015

PRE-MENOPAUSA

Figura 16 – CARCINOMA MAMMARIO METASTATICO

Terapia ormonale in pre-menopausa



Legenda - LH-RH = Luteinizing Hormone-Release Hormone; **AI=** inibitore dell'aromatasi; **classe di AI=** classe molecolare di AI non steroideo o steroideo.

Nota a - Intervallo tra la fine del trattamento con tamoxifene adiuvante e la comparsa di metastasi >12 mesi.

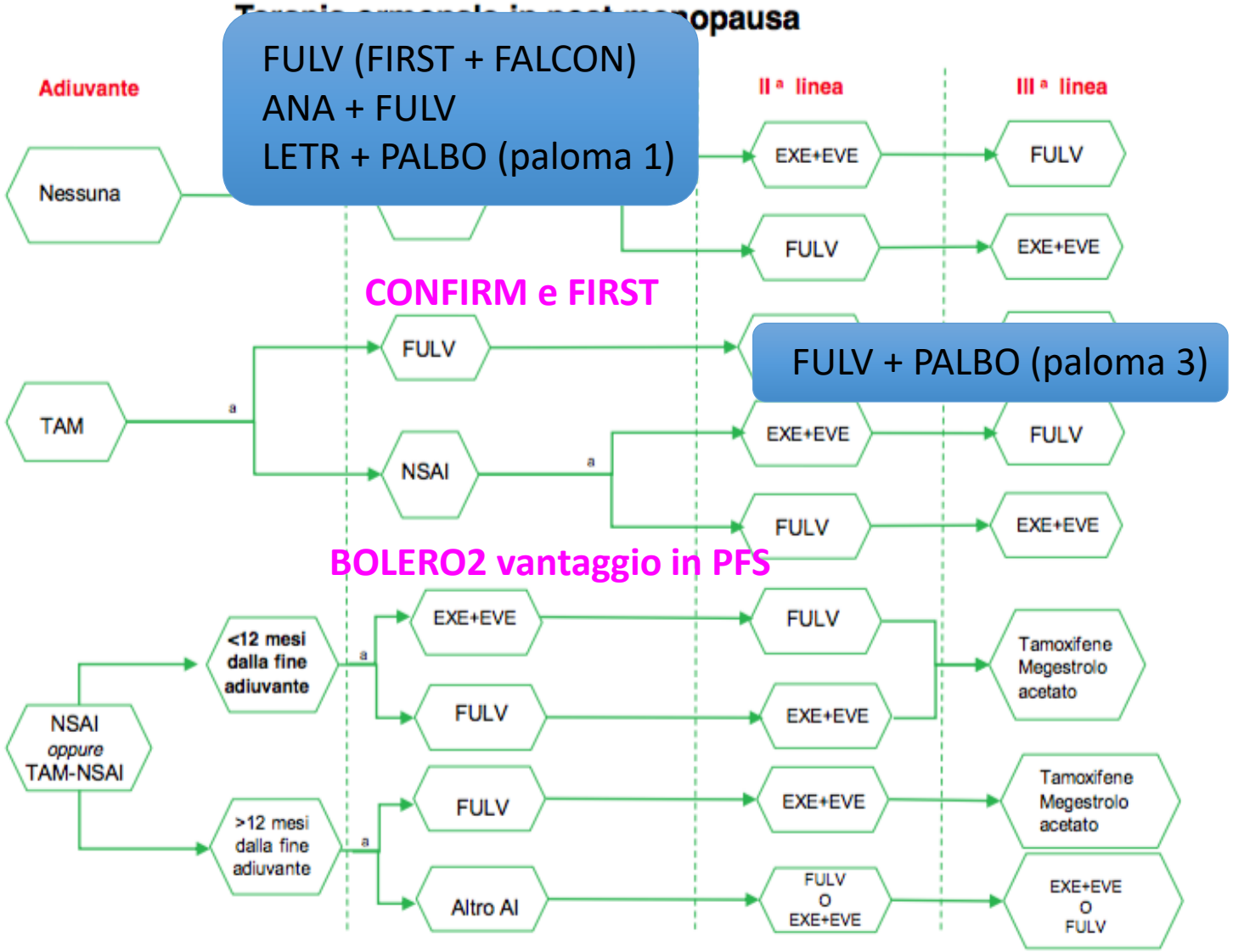
Nota b - Comparsa di metastasi durante il trattamento adiuvante oppure entro 12 mesi dalla fine del trattamento adiuvante con tamoxifene.

Nota c - Palbociclib in Italia è in fase Cnn (Classe C non rimborsabile) al momento della stesura di questa Linea Guida

Linee guida AIOM 2017

POST-MENOPAUSA

Figura 17 – CARCINOMA MAMMARIO METASTATICO



TAM= tamoxifene; **NSAI**= inibitore dell'aromatasi non steroideo (anastrozolo, letrozolo); **EXE**= exemestae; **EVE**=everolimus; **FULV**=fulvestrant

Note: a: per discussione su possibili criteri di scelta, vedi testo

Linee guida AIOM 2015

POST-MENOPAUSA

Figura 17 – CARCINOMA MAMMARIO METASTATICO

Terapia ormonale in post-menopausa

Adiuvante		1° linea	2° linea	3° linea
Nessuna		**Fulvestrant** **NSAI** **Letrozolo-Palbociclib[1]**	**Fulvestrant-Palbociclib[2]** **Everolimus-exemestane[3]** **Fulvestrant**	NE**
TAM TAM > NSAI/SAI NSAI/SAI	Ripresa tardiva (>12 mesi dalla fine adiuvante)	**Letrozolo-Palbociclib[1]** **Fulvestrant** **NSAI/SAI[4]**	**Everolimus-exemestane[3]** **Fulvestrant-Palbociclib[2]**	NE**
TAM TAM > NSAI/SAI NSAI/SAI	Ripresa precoce (<12 mesi dalla fine adiuvante) QUESITO 15	**Fulvestrant-Palbociclib[2]** **Everolimus-exemestane[3]** **Fulvestrant**	**Fulvestrant** **Everolimus-exemestane[3]**	NE**

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

Nota 1= Palbocilcib in Italia è in fase Cnn (Classe C non rimborsabile) al momento della stesura di questa Linea Guida
Nota 2 = In base a registrazione EMA
Nota 3= Everolimus prescrivibile solo dopo ricaduta o progressione a seguito di un trattamento con NSAI
Nota 4= In casi selezionati, con recidive molto tardive
Legenda: NSAI= Inibitori non steroidei dell'aromatasi (letrozolo, anastrozolo); SAI=Inibitori steroidei dell'aromatasi (Exemestane)

Consulta il quesito clinico n. 15

Linee guida AIOM 2017

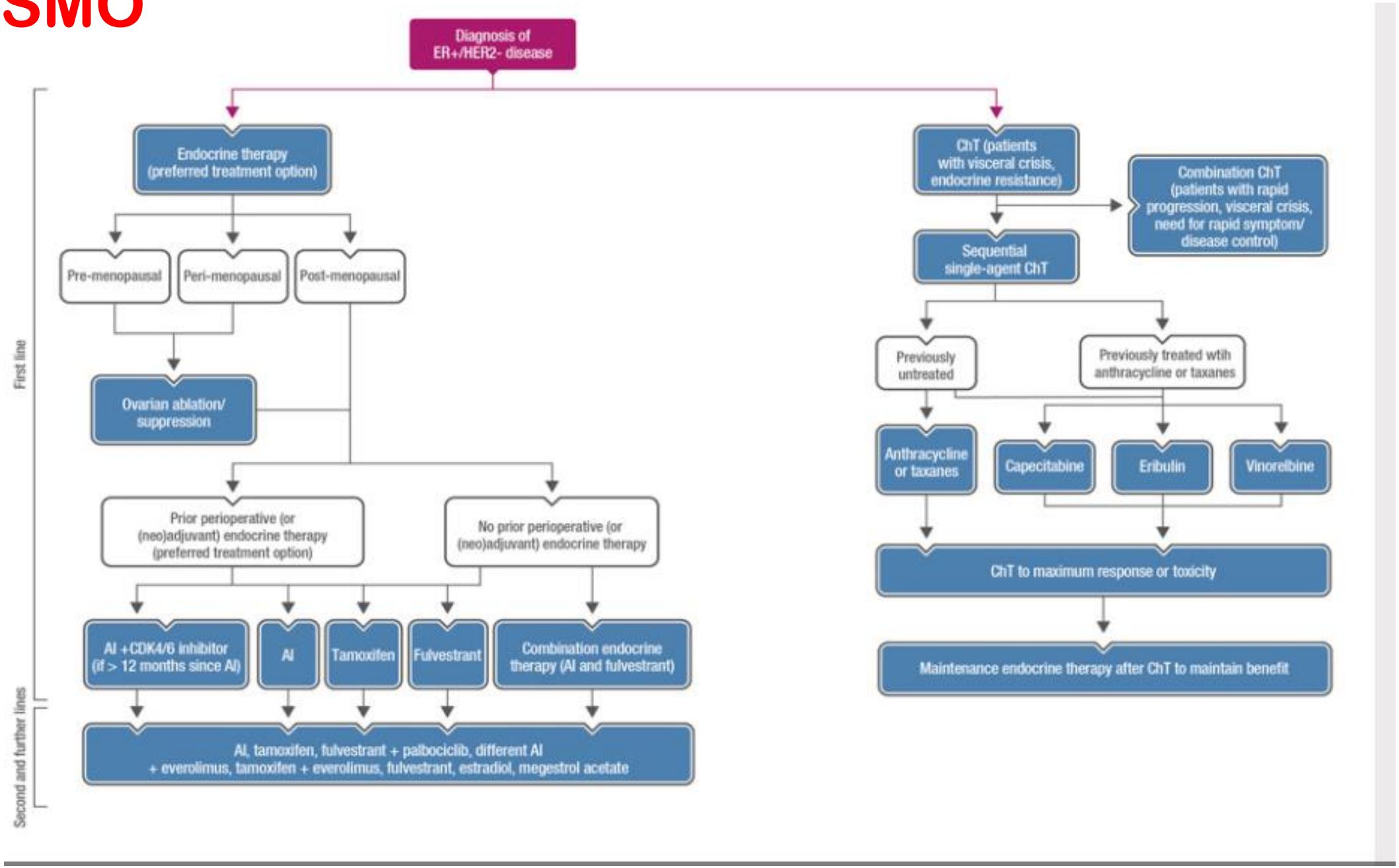
Annals of Oncology 28: 16–33, 2017
doi:10.1093/annonc/mdw544
Published online 5 December 2016

SPECIAL ARTICLE

3rd ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3)

F. Cardoso[1*], A. Costa[2], E. Senkus[3], M. Aapro[4], F. André[5], C. H. Barrios[6], J. Bergh[7], G. Bhattacharyya[8], L. Biganzoli[9], M. J. Cardoso[10], L. Carey[11], D. Corneliussen-James[12], G. Curigliano[13], V. Dieras[14], N. El Saghir[15], A. Eniu[16], L. Fallowfield[17], D. Fenech[18], P. Francis[19], K. Gelmon[20], A. Gennari[21], N. Harbeck[22], C. Hudis[23], B. Kaufman[24], I. Krop[25], M. Mayer[26], H. Meijer[27], S. Mertz[28], S. Ohno[29], O. Pagani[30], E. Papadopoulos[31], F. Peccatori[32], F. Penault-Llorca[33], M. J. Piccart[34], J. Y. Pierga[35], H. Rugo[36], L. Shockney[37], G. Sledge[38], S. Swain[39], C. Thomssen[40], A. Tutt[41], D. Vorobiof[42], B. Xu[43], L. Norton[44] & E. Winer[45]

ESMO


Diagnosis of ER+/HER2- disease
Endocrine therapy (preferred treatment option)
Pre-menopausal
Peri-menopausal
Post-menopausal
Ovarian ablation/ suppression
Prior perioperative (or (neo)adjuvant) endocrine therapy (preferred treatment option)
No prior perioperative (or (neo)adjuvant) endocrine therapy
AI +CDK4/6 inhibitor (if > 12 months since AI)
AI
Tamoxifen
Fulvestrant
Combination endocrine therapy (AI and fulvestrant)
AI, tamoxifen, fulvestrant + palbociclib, different AI + everolimus, tamoxifen + everolimus, fulvestrant, estradiol, megestrol acetate
First line
Second and further lines
ChT (patients with visceral crisis, endocrine resistance)
Combination ChT (patients with rapid progression, visceral crisis, need for rapid symptom/ disease control)
Sequential single-agent ChT
Previously untreated
Previously treated wtih anthracycline or taxanes
Anthracycline or taxanes
Capecitabine
Eribulin
Vinorelbine
ChT to maximum response or toxicity
Maintenance endocrine therapy after ChT to maintain benefit

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28: 16–33, 2017
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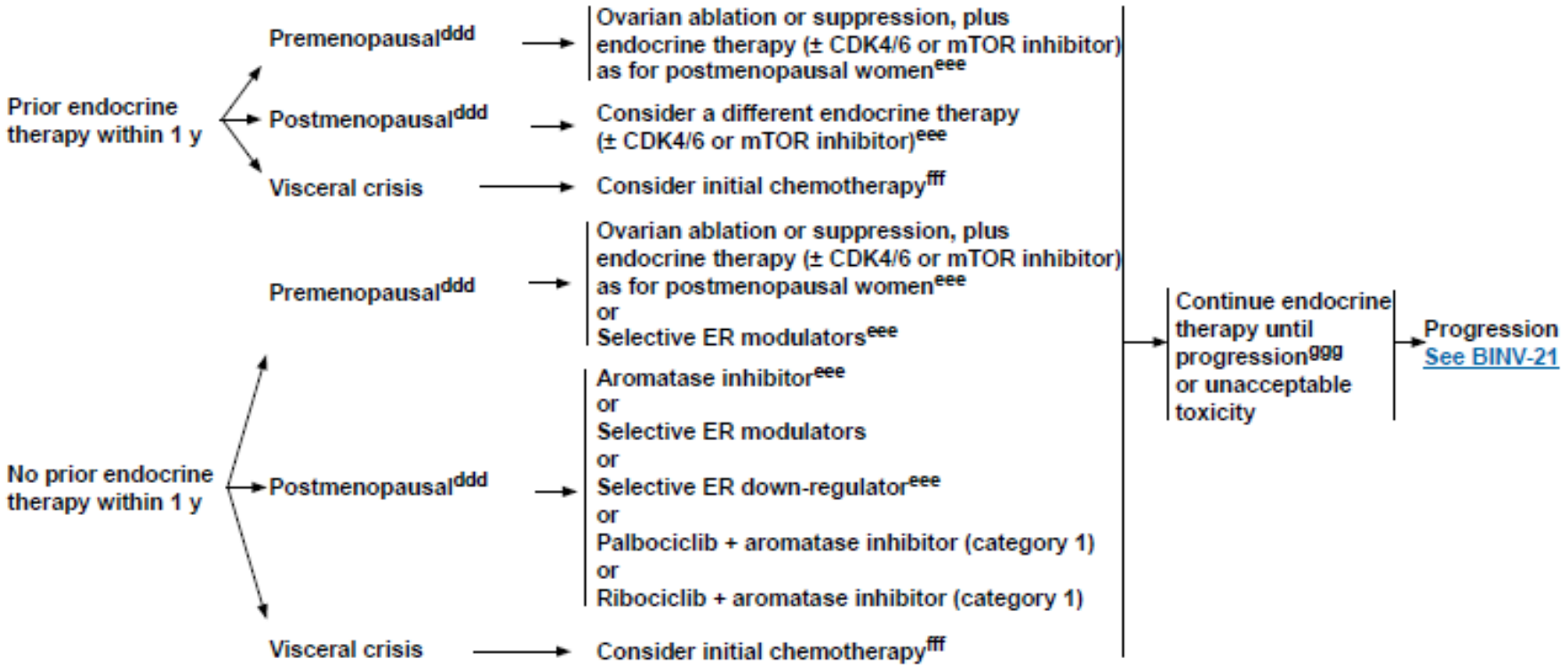
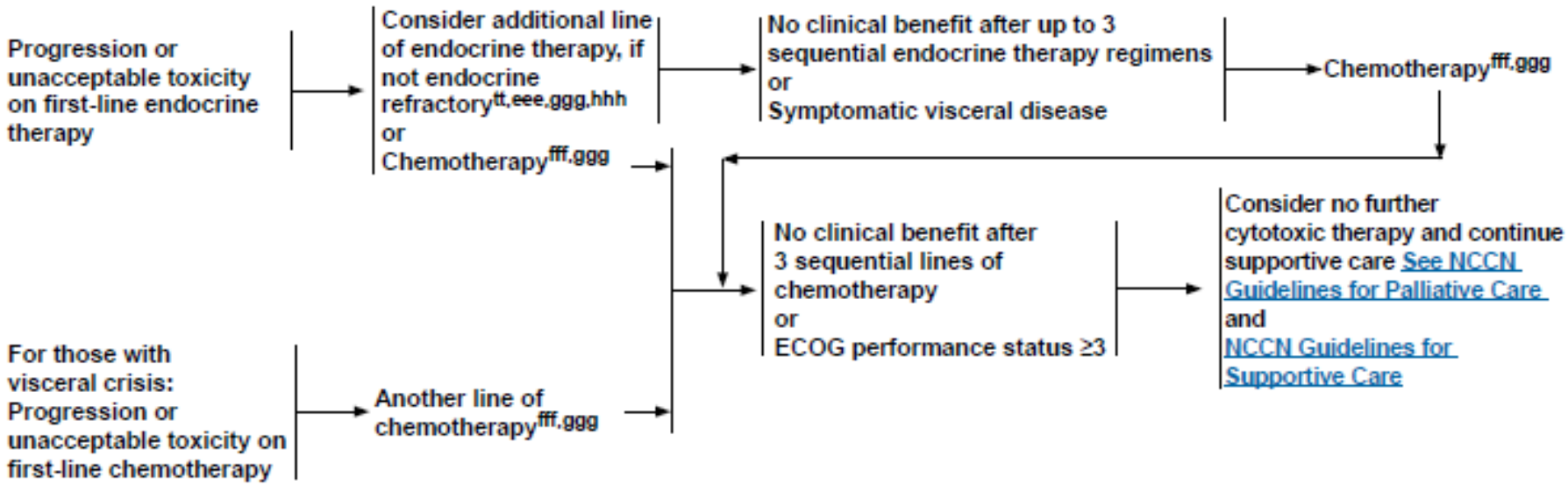
The optimal sequence of single endocrine agents and combinations with targeted agents is currently unknown and is a research priority. It is crucial to collect data from clinical trials beyond progression to better understand the efficacy of each class of agent when given after the other

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE
ER and/or PR POSITIVE; HER2 NEGATIVE[c]



[c] See Principles of HER2 Testing (BINV-A).
[ddd] See Definition of Menopause (BINV-M).
[eee] See Systemic Therapy for ER and/or PR Positive Recurrent or Stage IV Disease (BINV-N).
[fff] See Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-O).
[ggg] See Principles of Monitoring Metastatic Disease (BINV-P).

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE
ER and/or PR POSITIVE; HER2 NEGATIVE[c]



[c] See Principles of HER2 Testing (BINV-A).

[tt] False-negative ER and/or PR determinations occur, and there may be discordance between the ER and/or PR determination between the primary and metastatic tumor(s). Therefore, endocrine therapy may be considered in patients with non-visceral or asymptomatic visceral tumors, especially in patients with clinical characteristics predicting for a hormone receptor-positive tumor (eg, long disease-free interval, limited sites of recurrence, indolent disease, older age).

[eee] See Systemic Therapy for ER and/or PR Positive Recurrent or Stage IV Disease (BINV-N).

[fff] See Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-O).

[ggg] See Principles of Monitoring Metastatic Disease (BINV-P).

[hhh] If 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.

SYSTEMIC THERAPY FOR ER and/or PR-POSITIVE RECURRENT OR STAGE IV DISEASE

Premenopausal and HER2-negative
- Selective ER modulators (tamoxifen or toremifene) or ovarian ablation or suppression plus endocrine therapy as for postmenopausal women

Postmenopausal and HER2-negative
- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Steroidal aromatase inactivator (exemestane)
- Exemestane + everolimus[1,2]
- Everolimus + fulvestrant
- Everolimus + tamoxifen
- Palbociclib + aromatase inhibitor (category 1)[2,3]
- Palbociclib + fulvestrant (category 1)[2,4]
- Ribociclib + aromatase inhibitor (category 1)[2,3]
- Abemaciclib + fulvestrant (category 1)[2,5]
- Selective ER down-regulator (fulvestrant, category 1)[6]
- Tamoxifen or toremifene
- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol
- Abemaciclib[2,7]

Premenopausal and HER2-positive
- Tamoxifen ± trastuzumab or
- Ovarian ablation or suppression plus therapy as for post-menopausal women

Postmenopausal and HER2-positive
- Aromatase inhibitor ± trastuzumab
- Aromatase inhibitor ± lapatinib
- Aromatase inhibitor ± lapatinib + trastuzumab
- Fulvestrant ± trastuzumab
- Tamoxifen ± trastuzumab

See Evidence Blocks on BINV-N (EB-1)

[1]A 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).

[2]If 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.

[3]Palbociclib or ribociclib in combination with an aromatase inhibitor (anastrozole, letrozole, or exemestane) may be considered as a treatment option for first-line therapy for postmenopausal patients with hormone-receptor positive, HER2-negative metastatic breast cancer.

[4]For postmenopausal women or for premenopausal women receiving ovarian suppression with an LHRH agonist, with hormone-receptor positive and HER2-negative metastatic breast cancer that has progressed on or after prior adjuvant or metastatic endocrine therapy.

[5]Indicated after progression on prior endocrine therapy.

[6]A 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.

[7]Indicated after progression on prior endocrine therapy and prior chemotherapy in the metastatic setting.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.

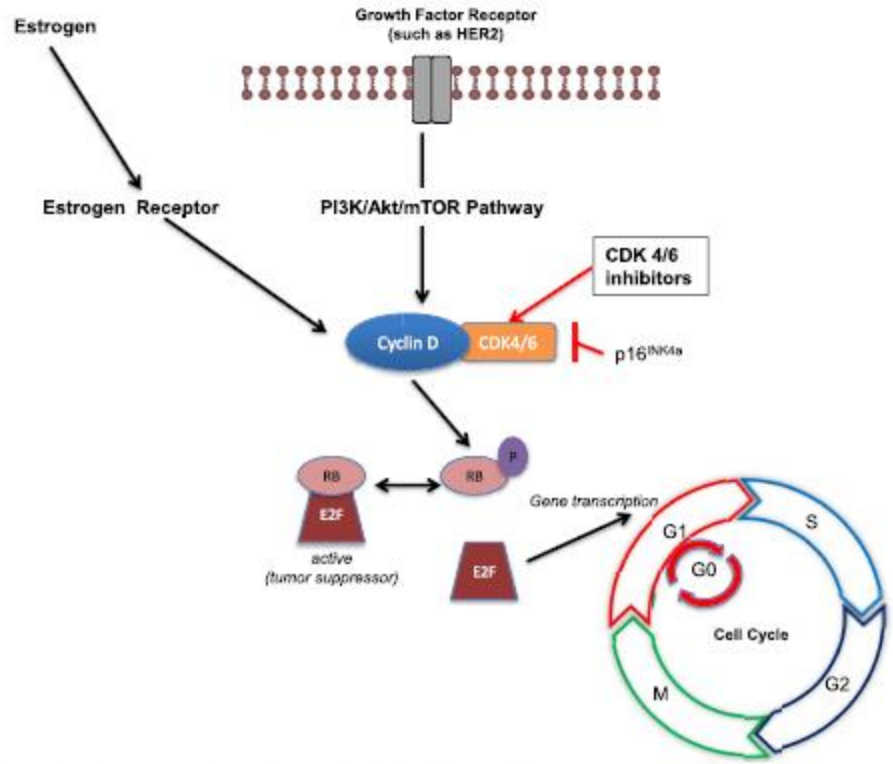


Figure 1. Role of cyclin-dependent kinase 4/6 inhibitors in halting cellular division.

Abbreviations: Akt, protein kinase B; CDK, cyclin-dependent kinase; E2F, E2 factor; G, growth; HER2, human epidermal growth factor receptor 2; M, mitosis; mTOR, mechanistic target of rapamycin; P, phosphate; PI3K, phosphoinositide 3-kinase; RB, retinoblastoma tumor suppressor protein; S, synthesis.

Comparative Potency of Selective CDK4/6 Inhibitors

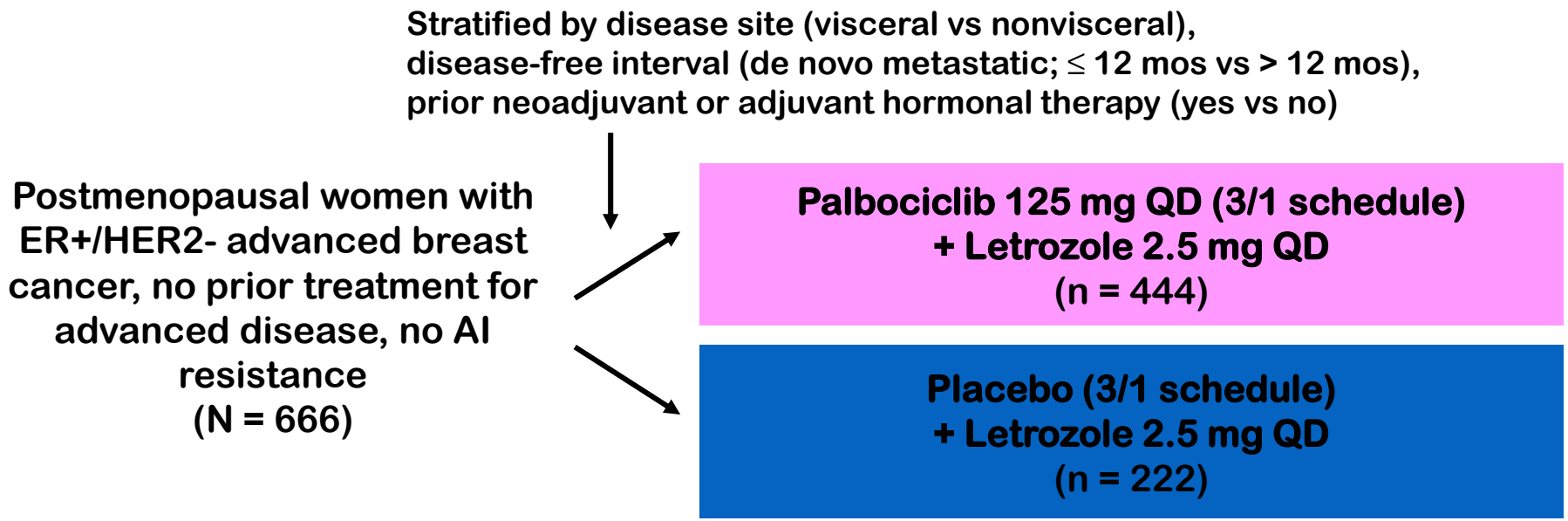
Agent	Cyclin-Dependent Kinase IC_{50}, nM		
	CDK4	CDK6	CDK9
Abemaciclib	2	9.9	57
Palbociclib	11	15	NR
Ribociclib	10	39	NR

- **These agents show little or no inhibitory activity for CDK1, CDK2, CDK5, or CDK7**

Gelbert LM, et al. Invest New Drugs. 2014;32:825-837. Fry DW, et al. Mol Cancer Ther. 2004;3:1427-1438. Kim S, et al. AACR-NCI-EORTC 2013. Abstract PR02.

PALOMA 2 :Phase III, Double-blind, Placebo-controlled Study of Palbociclib + Letrozole

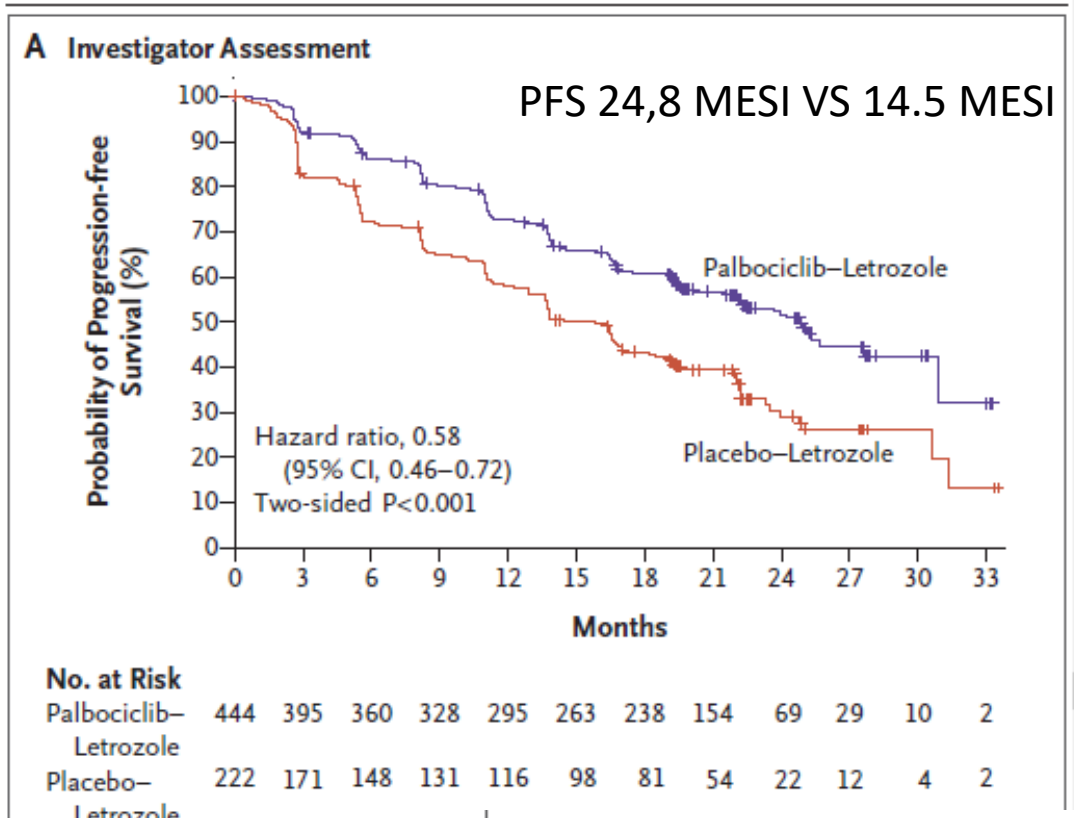
Multicenter, international, double-blind, randomized phase III trial



Primary endpoint: PFS by investigator
Secondary endpoints: response, OS, safety, biomarkers, pt-reported outcomes

Finn R, et al. ASCO 2016. Abstract 507.

PALOMA-2:



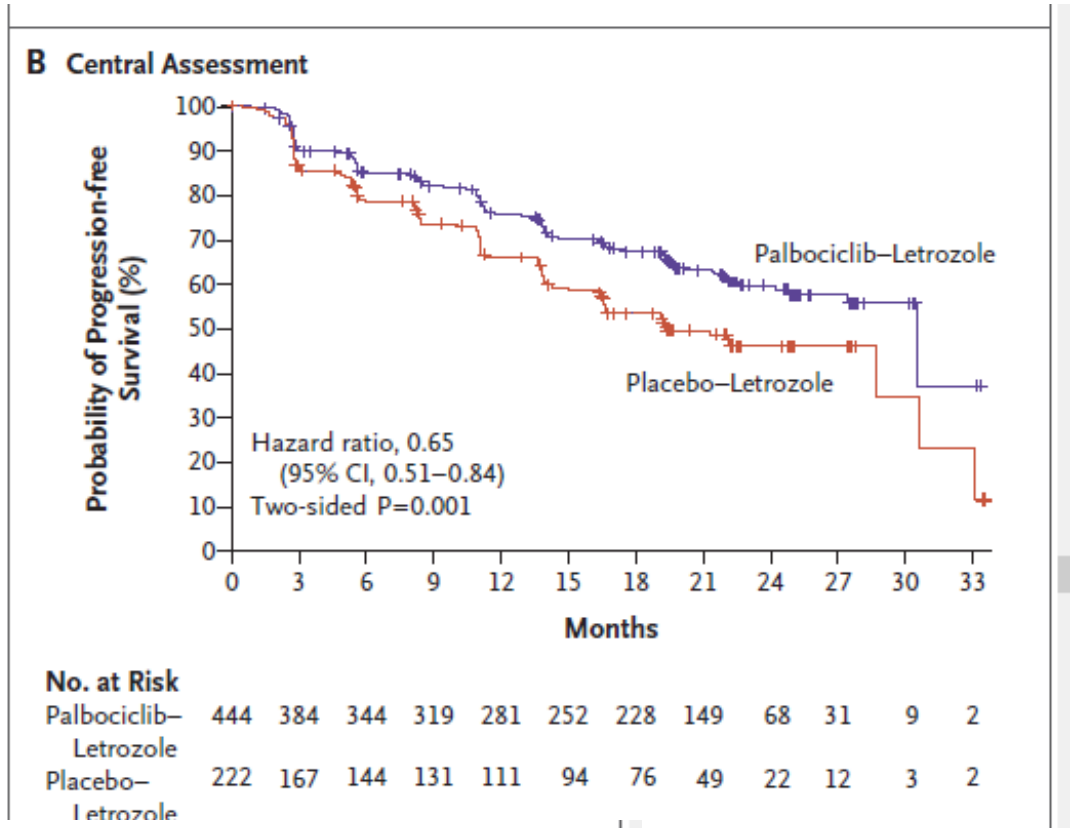


Figure 1. Progression-free Survival.

Panel A shows progression-free survival in the intention-to-treat population, as assessed by the investigators (primary analysis); the median progression-free survival was 24.8 months (95% CI, 22.1 to not estimable) among the 444 patients in the palbociclib–letrozole group and 14.5 months (95% CI, 12.9 to 17.1) among the 222 patients in the placebo–letrozole group. Panel B shows progression-free survival in the intention-to-treat population, as assessed by means of blinded, independent central review; the median progression-free survival was 30.5 months (95% CI, 24.7 to not estimable) among the 444 patients in the palbociclib–letrozole group and 19.3 months (95% CI, 16.4 to 30.6) among the 222 patients in the placebo–letrozole group.

PALOMA-2:

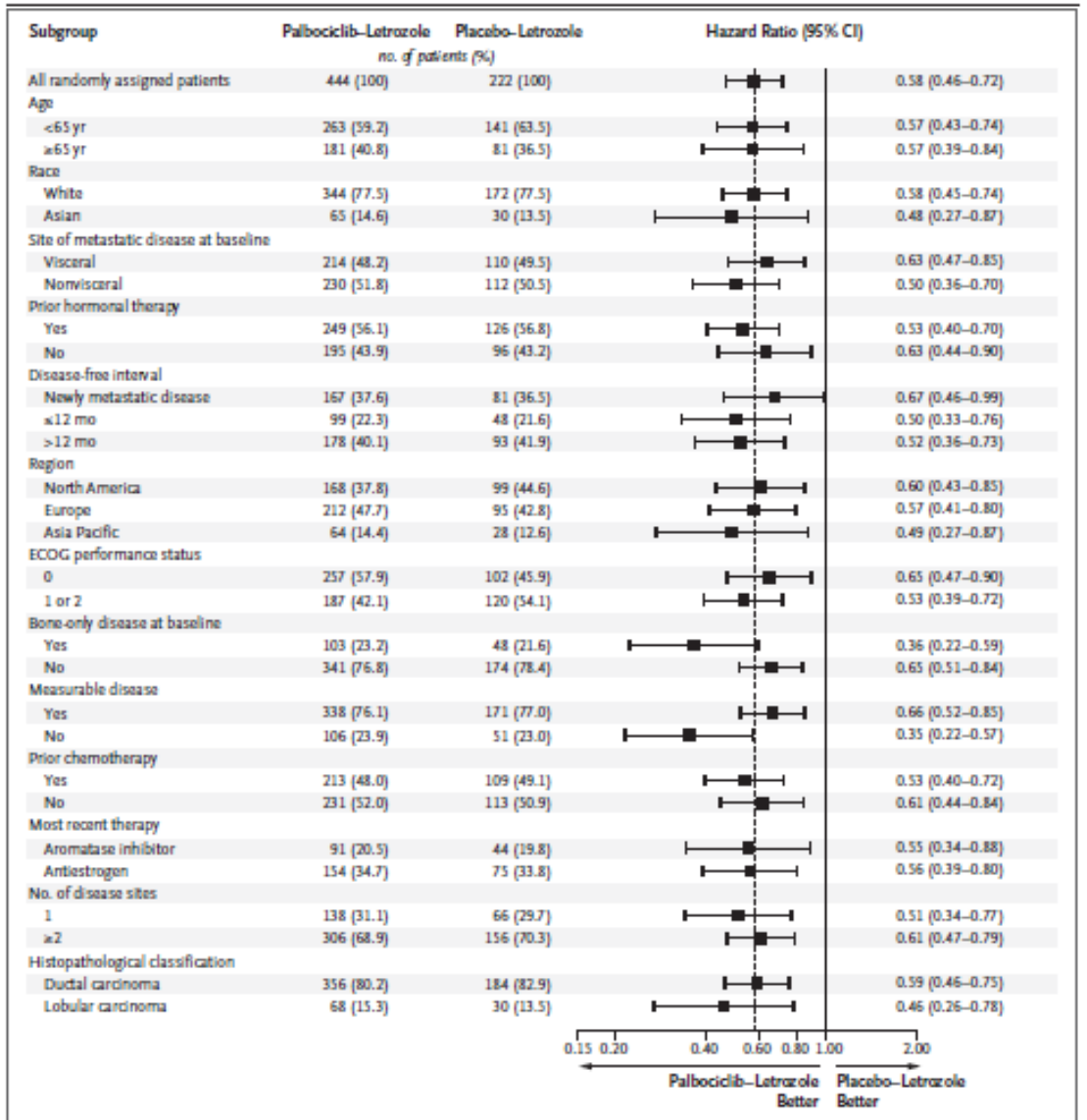


Figure 2. Subgroup Analysis of Progression-free Survival.

Shown are the hazard ratios with 95% confidence intervals for disease progression or death in various subgroups. Newly metastatic disease (referred to as "de novo metastatic" in the protocol) applies to patients who had not received any prior systemic therapy, for whom a determination of disease-free interval was not possible. Eastern Cooperative Oncology Group (ECOG) performance status is measured on a 5-point scale, with 0 indicating no symptoms and higher numbers indicating increasing disability. Ductal carcinoma includes diffuse adenocarcinoma, mixed adenocarcinoma, adenocarcinoma and ductal carcinoma. Data from patients with miscellaneous histopathological features are not reported owing to the small sample size.

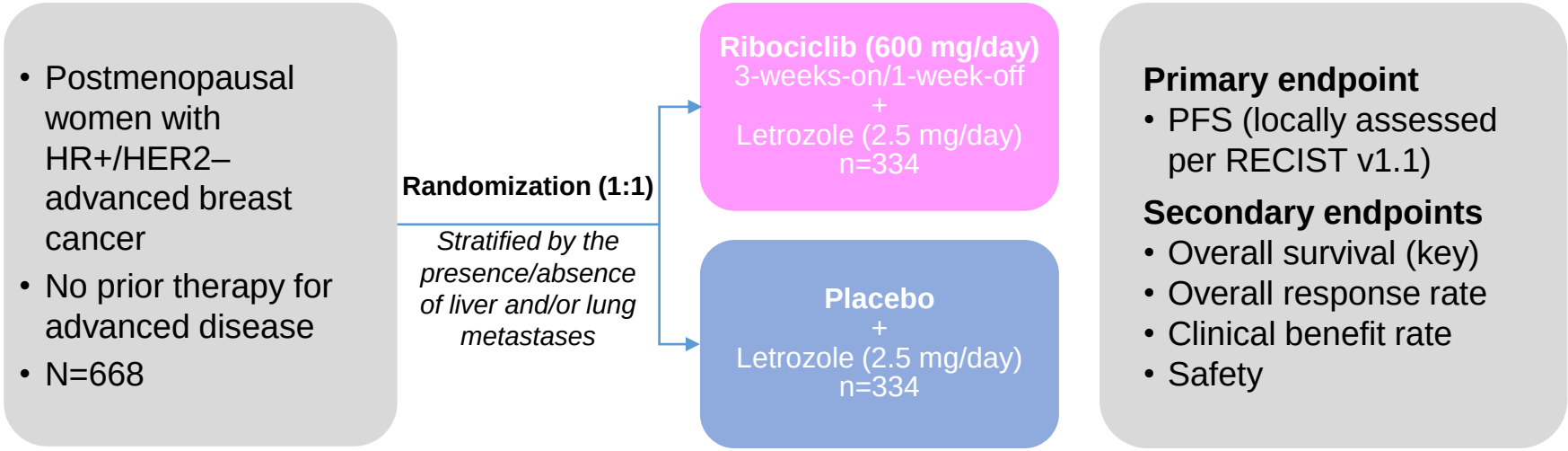
PALOMA-2:

Table 3. Best Overall Response in the Intention-to-Treat Population.

Variable	Palbociclib–Letrozole (N=444)	Placebo–Letrozole (N=222)	Odds Ratio (95% CI)	P Value
All randomly assigned patients — no.	444	222		
Rate of objective response — % (95% CI)*	42.1 (37.5–46.9)	34.7 (28.4–41.3)	1.40 (0.98–2.01)	0.06
Rate of clinical benefit response — % (95% CI)†	84.9 (81.2–88.1)	70.3 (63.8–76.2)	2.39 (1.58–3.59)	<0.001
Median duration of response — mo (95% CI)	22.5 (19.8–28.0)	16.8 (14.2–28.5)‡		
Patients with measurable disease — no.§	338	171		
Rate of objective response — % (95% CI)*	55.3 (49.9–60.7)	44.4 (36.9–52.2)	1.55 (1.05–2.28)	0.03
Rate of clinical benefit response — % (95% CI)†	84.3 (80.0–88.0)	70.8 (63.3–77.5)	2.23 (1.39–3.56)	<0.001
Median duration of response — mo (95% CI)	22.5 (19.8–28.0)	16.8 (15.4–28.5)		

* Rate of objective response was defined as the percentage of patients who had a confirmed complete response or a partial response.
† Rate of clinical benefit response was defined as the percentage of patients who had a confirmed complete response, a partial response, or stable disease for 24 weeks or more.
‡ One patient with bone-only disease at baseline was included; all other patients had measurable disease at baseline.
§ Measurable disease was defined according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[8]

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 α=2.5%
- Interim analysis planned after ~70% PFS events
  - Two-look Haybittle–Peto stopping criteria: hazard ratio ≤0.56 and p<0.0000129

- PFS, progression-free survival.
- MONALEESA-2 is registered at ClinicalTrials.gov (NCT01958021).

Progression free survival

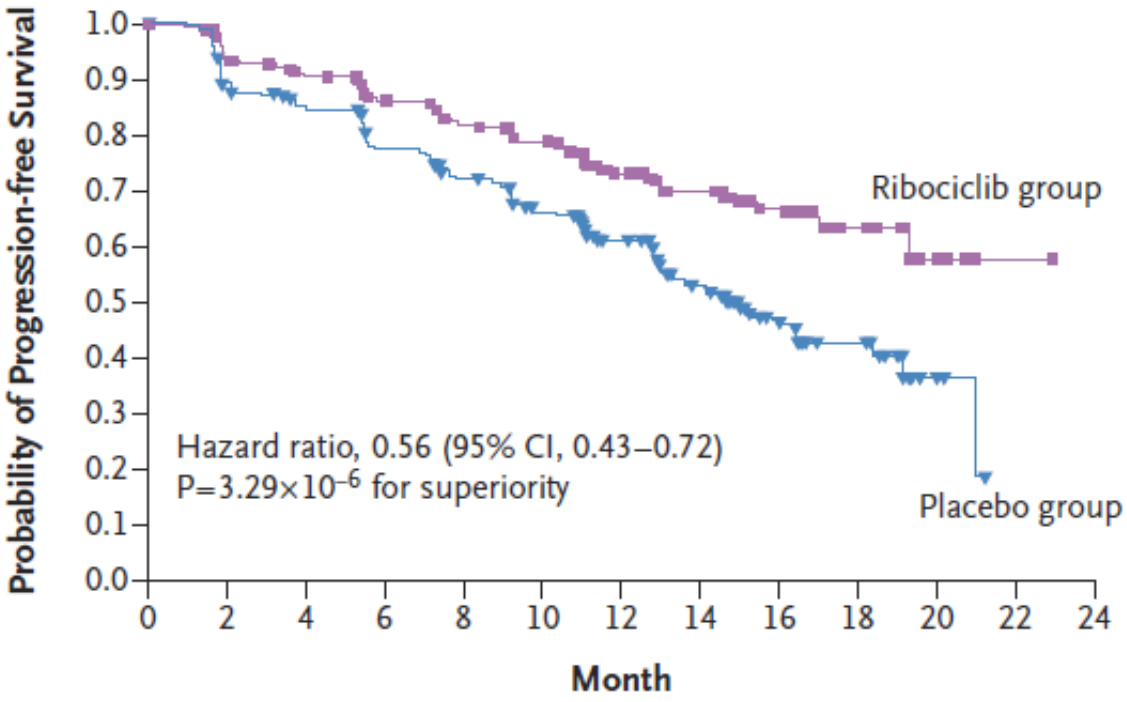


Figure 1. Kaplan–Meier Analysis of Progression-free Survival.

After 18 months, the progression-free survival rate was 63.0% (95% CI, 54.6 to 70.3) in the ribociclib group and 42.2% (95% CI, 34.8 to 49.5) in the placebo group. The median duration of progression-free survival was not reached in the ribociclib group and was 14.7 months in the placebo group.

N Engl J Med. 2016 Nov 3;375(18):1738-1748.

MONALEESA-2:

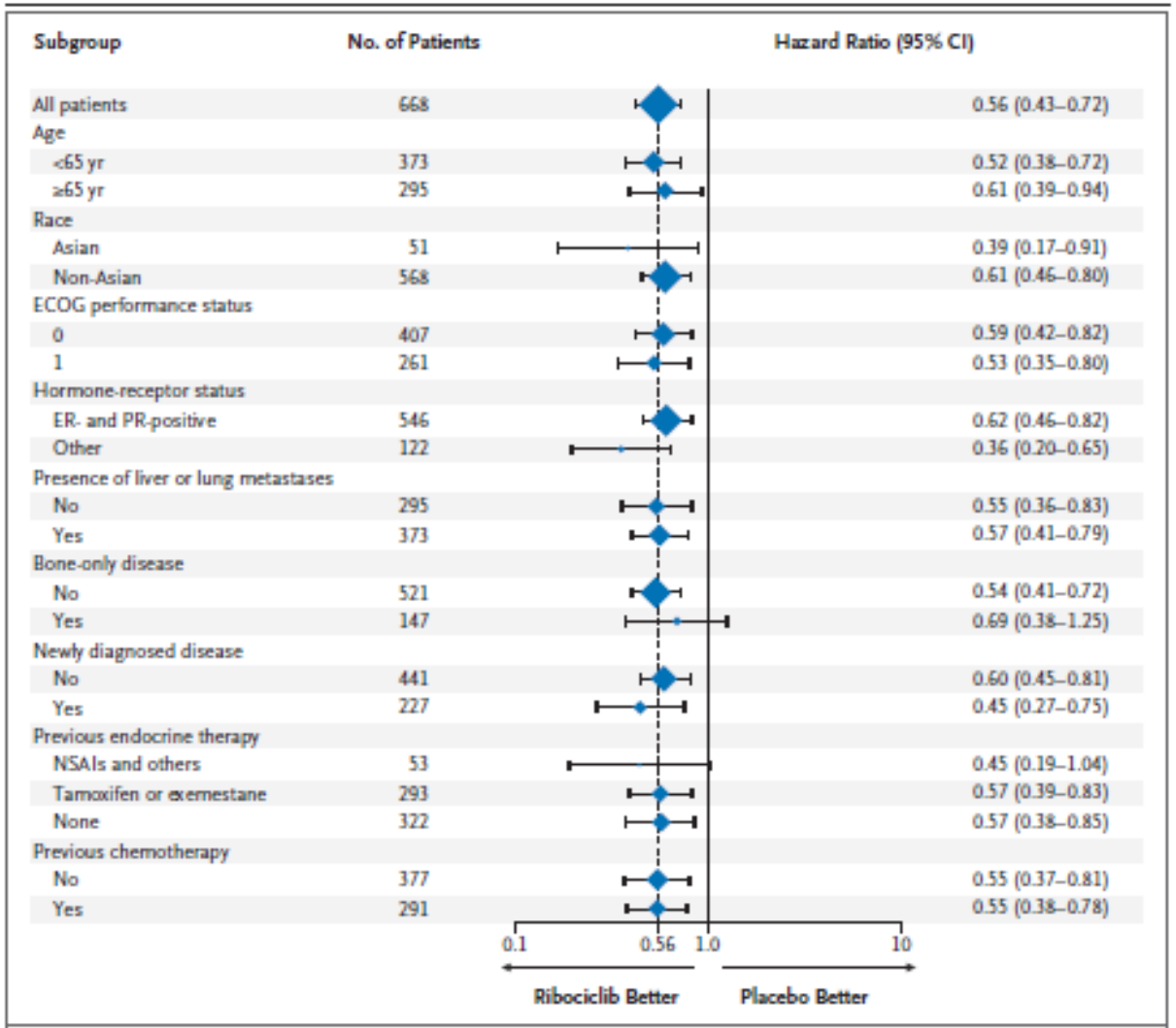


Figure 2. Subgroup Analysis of Progression-free Survival.

The progression-free survival benefit in the ribociclib group (as assessed by investigators) was observed across all predefined subgroups (overall hazard ratio, 0.56; 95% CI, 0.43 to 0.72; $P<3.29\times10^{-6}$ for superiority) (dashed line). Among the patients who had received previous endocrine therapy, those taking nonsteroidal aromatase inhibitors (NSAIs) or other therapies not listed here had not received tamoxifen. Previous endocrine therapy and chemotherapy include neoadjuvant and adjuvant treatment. The size of the data points is proportional to the number of patients included in the subgroup analysis. ECOG denotes Eastern Cooperative Oncology Group.

N Engl J Med. 2016 Nov 3;375(18):1738-1748.

MONALEESA-2:

Table 2. Best Overall Response, According to Local Assessment.

Response	Ribociclib Group	Placebo Group
All patients — no.	334	334
Confirmed best overall response — no. (%)		
Complete response	9 (2.7)	7 (2.1)
Partial response	127 (38.0)	85 (25.4)
Stable disease	95 (28.4)	111 (33.2)
Neither complete response nor progressive disease*	66 (19.8)	75 (22.5)
Progressive disease	19 (5.7)	40 (12.0)
Unknown	18 (5.4)	16 (4.8)
Overall response†		
No. of patients	136	92
Percentage of patients (95% CI)	40.7 (35.4–46.0)	27.5 (22.8–32.3)
Clinical benefit‡		
No. of patients	266	243
Percentage of patients (95% CI)	79.6 (75.3–84.0)	72.8 (68.0–77.5)
Patients with measurable disease at baseline — no.	256	245
Confirmed best overall response — no. (%)		
Complete response	8 (3.1)	6 (2.4)
Partial response	127 (49.6)	85 (34.7)
Stable disease	95 (37.1)	111 (45.3)
Progressive disease	13 (5.1)	31 (12.7)
Unknown	13 (5.1)	11 (4.5)
Overall response†		
No. of patients	135	91
Percentage of patients (95% CI)	52.7 (46.6–58.9)	37.1 (31.1–43.2)
Clinical benefit§		
No. of patients	205	176
Percentage of patients (95% CI)	80.1 (75.2–85.0)	71.8 (66.2–77.5)

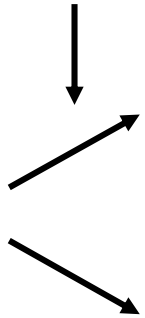
* In this category, the best overall response was evaluated only among patients who had no measurable disease at baseline, according to the Response Evaluation Criteria in Solid Tumors, version 1.1. One patient with measurable disease in the placebo group was misclassified as having a best overall response of neither complete response nor progressive disease.
† Overall response included a complete or partial response ($P<0.001$ for the comparison with placebo).
‡ Clinical benefit in the overall population was defined as a complete or partial response, stable disease lasting 24 weeks or more, or neither a complete response nor progressive disease lasting 24 weeks or more ($P=0.02$ for the comparison with placebo).
§ Clinical benefit among patients with measurable disease at baseline was defined as a complete or partial response or stable disease lasting 24 weeks or more ($P=0.02$ for the comparison with placebo).

N Engl J Med. 2016 Nov 3;375(18):1738-1748.

First-line Abemaciclib + AI Therapy in HR+, HER2- Advanced BC (MONARCH 3)

Stratified by metastatic site (visceral vs bone only vs other), previous ET (AI vs no ET vs other)

Postmenopausal women with HR+, HER2- metastatic or locally recurrent BC, no earlier systemic tx in this setting, DFS > 12 mos since ET (if received neo/adj ET), ECOG PS 0/1 (N = 493)



Abemaciclib 150 mg BID continuous + **NSAI** (physician's choice*) (n = 328)

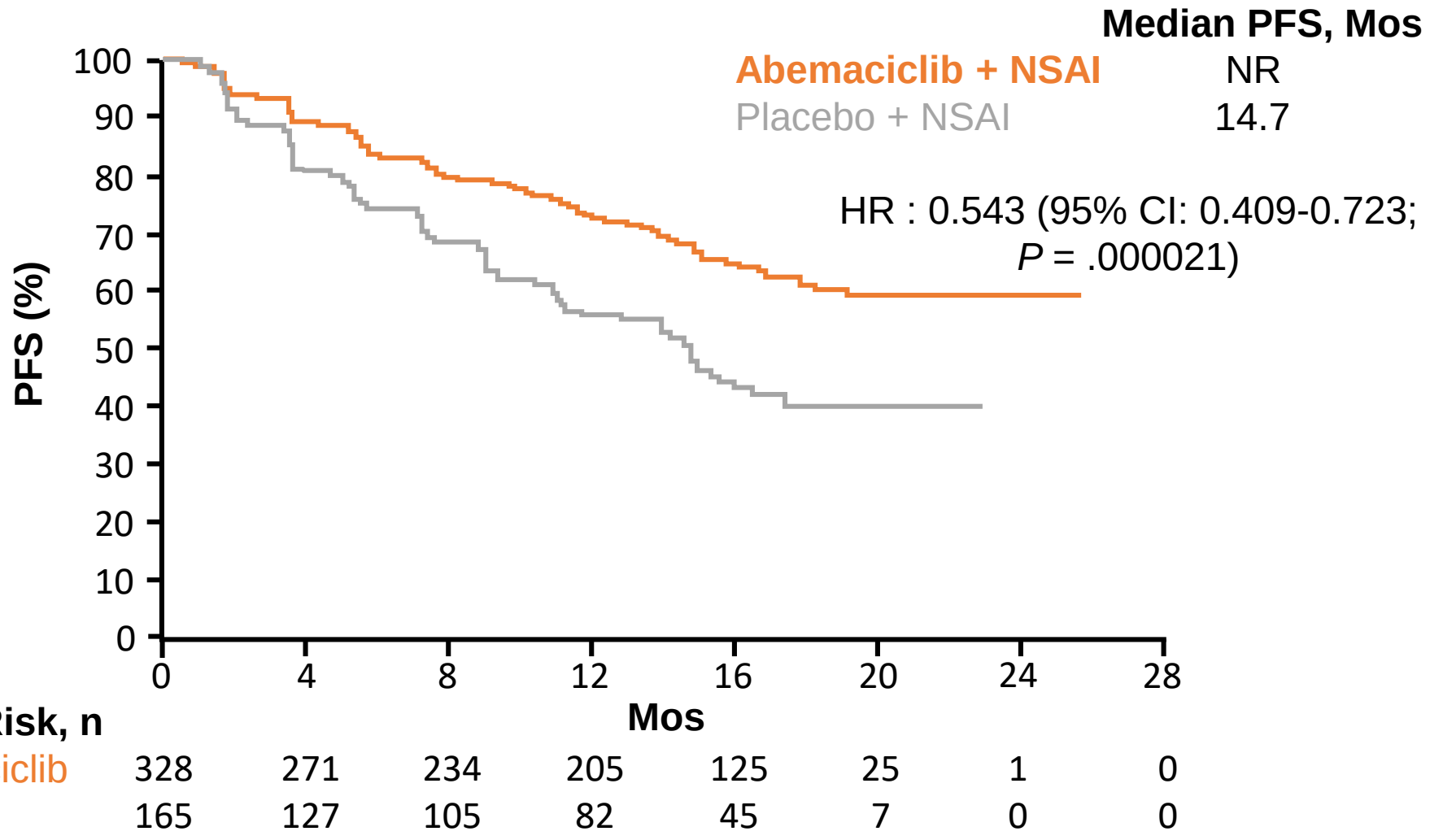
Placebo BID continuous + **NSAI** (physician's choice*) (n = 165)

*Physician's choice of anastrozole (1 mg) or letrozole (2.5 mg QD until PD).

- Primary endpoint: investigator-assessed PFS
- Secondary endpoints: OS, response rate, safety
- Interim analysis after median follow-up of 17.8 mos

Di Leo A, et al. ESMO 2017. Abstract 236O_PR.

MONARCH 3: Interim Analysis of PFS



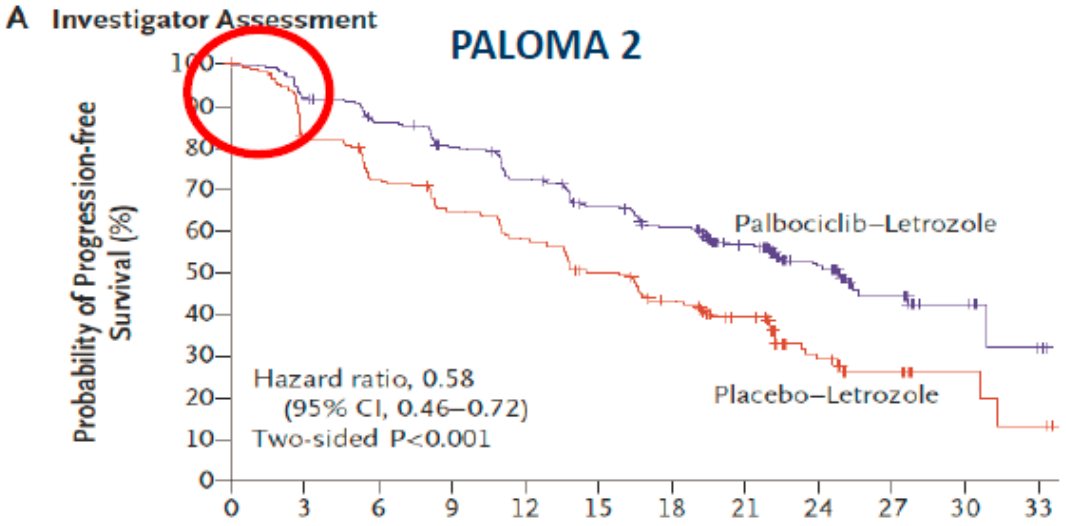
Di Leo A, et al. ESMO 2017. Abstract 236O_PR. Reproduced with permission.

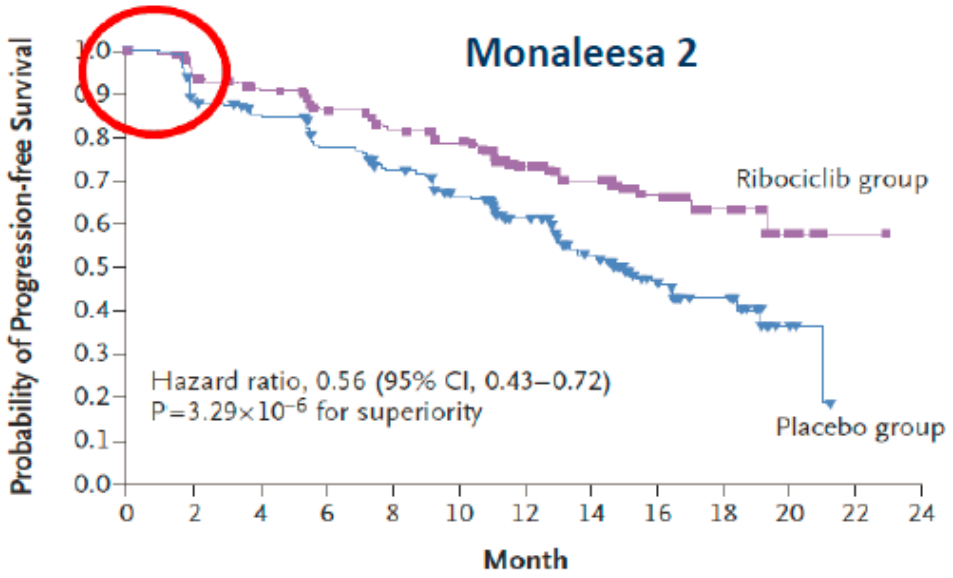
MONARCH 3: ORR and CBR

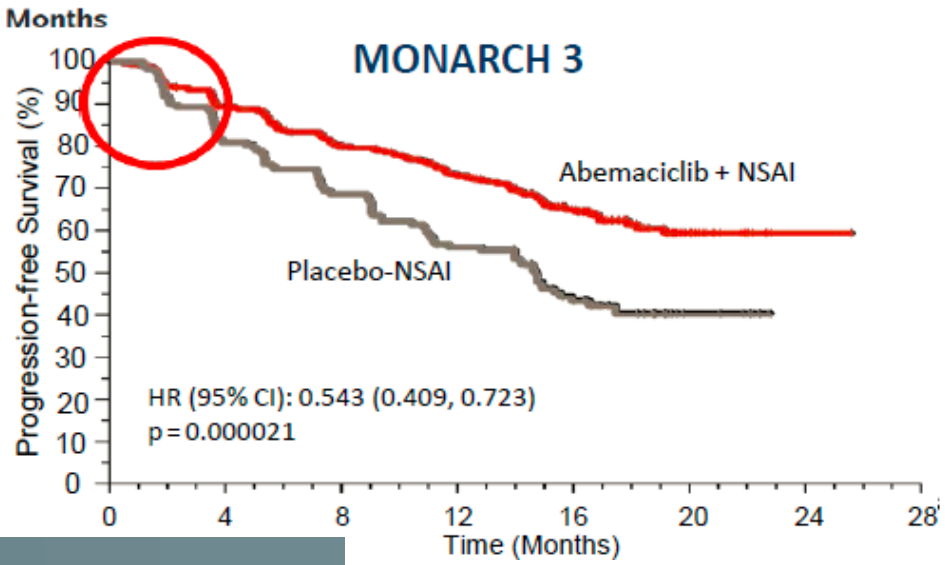
Response, %	Abemaciclib + NSAI	Pbo + NSAI	*P* Value
All pts	n = 328	n = 165	
ORR	48.2	34.5	.002
▪ CR	1.5	0	
CBR	78.0	71.5	.101
Pts with measurable baseline disease	n = 267	n = 130	
ORR	59.2	43.8	.004
▪ CR	1.9	0	
CBR	79.4	69.2	.024

Di Leo A, et al. ESMO 2017. Abstract 236O_PR.

PALOMA 2, Monaleesa 2 & MONARCH 3- PFS







Finn R, NEJM 2016; Hortobagyi GN, NEJM 2016; DiLeo A, ESMO 2017

HR+/HER2-ve ABC:
Activity of 1st Line Endocrine Therapy with Targeted Agents

option	ORR %	CBR %
Palbociclib + letrozole	**42 %**	85 %
Ribociclib + letrozole	**41 %**	80 %
Abemaciclib + NSAI	**48 %**	78 %

AIs + CDK4/6i induce a rapid tumor shrinkage comparable to that achievable with chemotherapy

HR+/HER2-ve ABC:
Activity of 1st Line Endocrine Therapy (w/o Targeted Agents)

option	ORR %	CBR %
AIs	**20-35%**	60 – 70 %
Fulv 250 + AI (endocrine-naive)	**27-32 %**	55 – 73 %
Fulv 500 (endocrine-naive)	**46 %**	78 %

Endocrine therapies induce a tumor shrinkage in a minority of patients and time to response may be long

Comparative Toxicities of CDK4/6 Inhibitors: Early Phase Trials

Adverse Event (All Grades), %	Palbociclib[1] (N = 37)	Ribociclib[2] (N = 67)	Abemaciclib[3] (N = 173)
Neutropenia	94	46	23
Anemia	70	28	20
Thrombocytopenia	76	34	23
Nausea	24	45	45
Vomiting	5	25	25
Diarrhea	16	27	63
Fatigue	68	33	41
QTc prolongation	No	9	No

1. DeMichele A, et al. Clin Cancer Res. 2015;21:995-1001.
2. Infante JR, et al. Clin Cancer Res. 2016;22:5696-5705.
3. Patnaik A, et al. Cancer Discov. 2016;6:740-753.

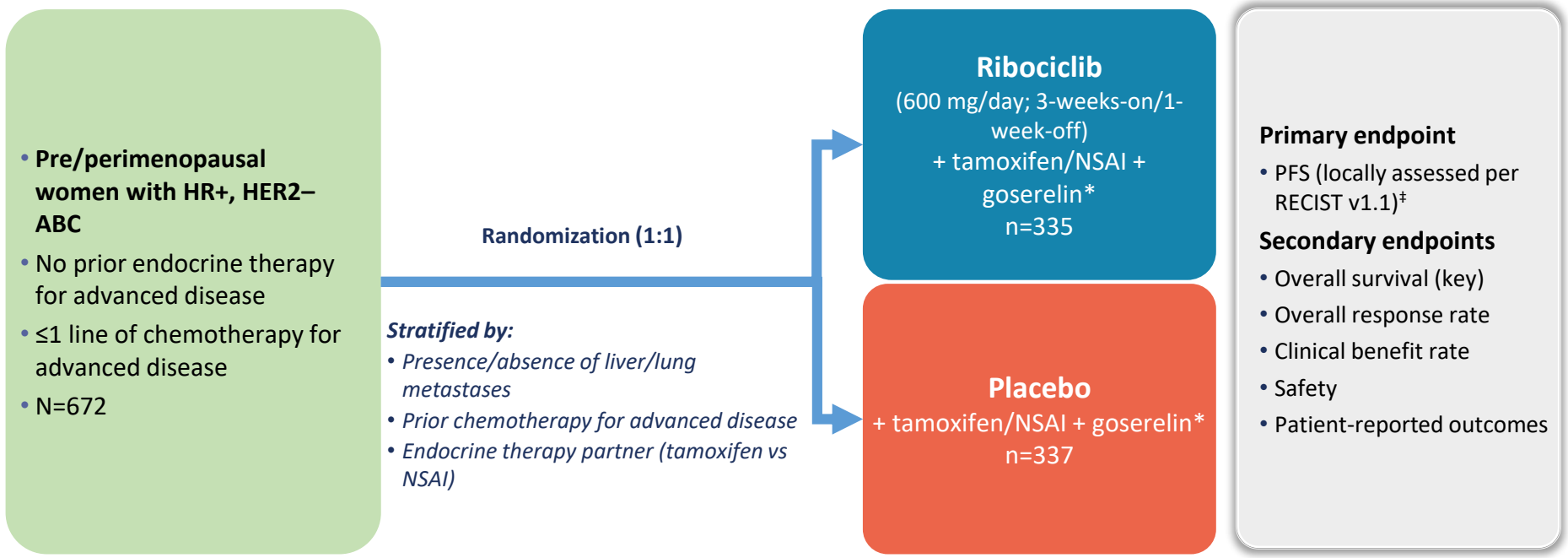
Results from the phase III MONALEESA-7 study

Dr. Tripathy

late breaking oral presentation

General session at SABCS 2017

MONALEESA-7: Phase III placebo-controlled study of ribociclib and tamoxifen/NSAI + goserelin



- Tumor assessments were performed every 8 weeks for 18 months, then every 12 weeks thereafter
- Primary analysis planned after ~329 PFS events

– 95% power to detect a 33% risk reduction (hazard ratio 0.67) with one-sided α=2.5%, corresponding to an increase in median PFS to 13.4 months (median PFS of 9 months for the placebo arm[1,2]), and a sample size of 660 patients

- NSAI, non-steroidal aromatase inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors.
- *Tamoxifen = 20 mg/day; NSAI: anastrozole = 1 mg/day or letrozole = 2.5 mg/day; goserelin = 3.6 mg every 28 days; ‡PFS by Blinded Independent Review Committee conducted to support the primary endpoint.

1. Klijn JG, *et al. J Clin Oncol* 2001;19:343–353; 2. Mourisden H, *et al. J Clin Oncol* 2001;19:2596–2606.

Key enrollment criteria

Key inclusion criteria

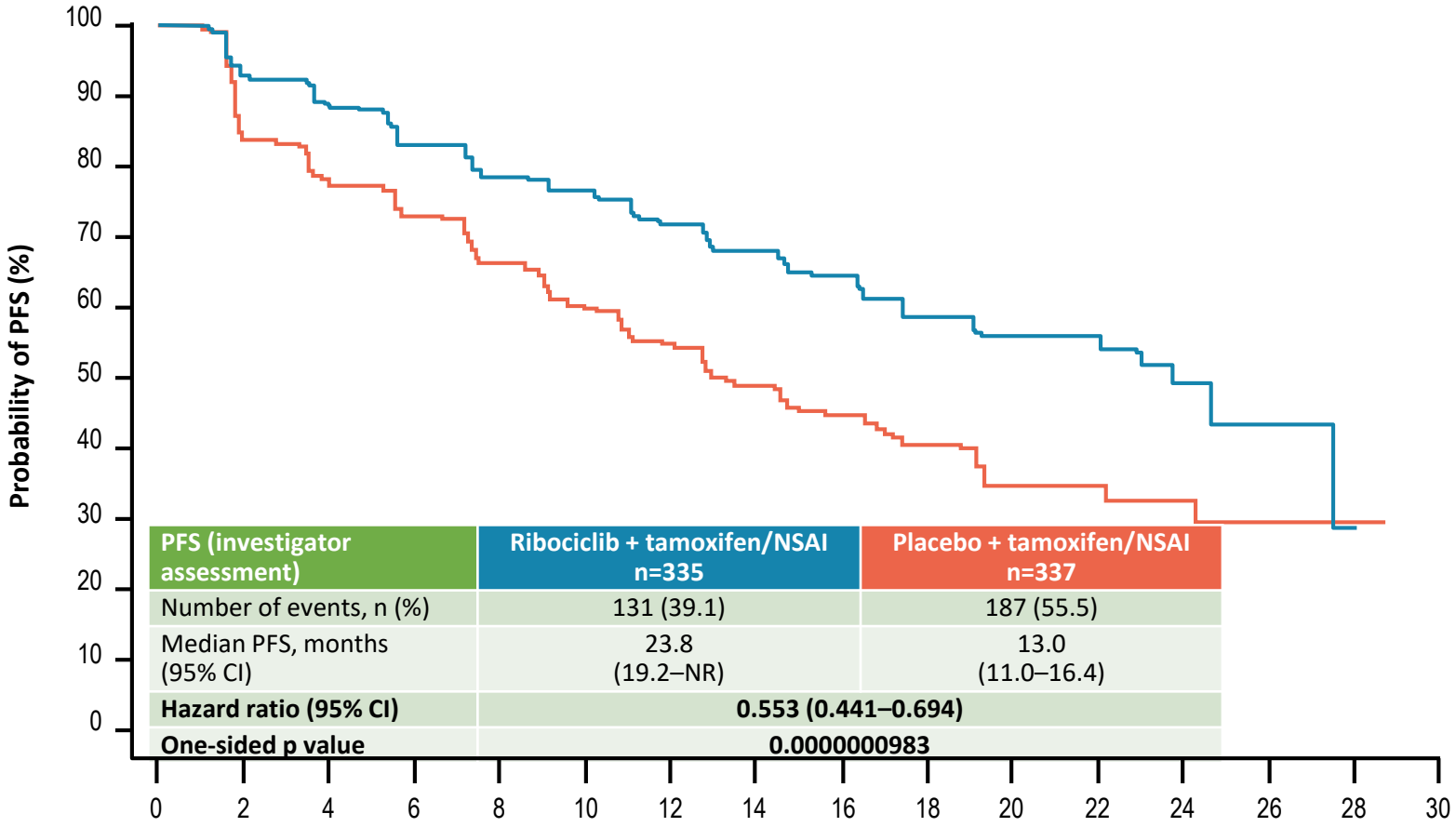
- Pre/perimenopausal women (per NCCN guidelines)
- ≥1 measurable lesion (RECIST 1.1) or ≥1 predominantly lytic bone lesion
- ECOG performance status of ≤1
- ≤1 line of chemotherapy for ABC
- Prior (neo)adjuvant therapy was allowed:
  - If no prior endocrine therapy OR if ≥12 months since the last dose, patient was eligible for tamoxifen or an NSAI, per investigator/patient choice
  - If last dose of tamoxifen was <12 months prior to randomization, patient was eligible for an NSAI
  - If last dose of AI/NSAI was <12 months prior to randomization, patient was eligible for tamoxifen

Key exclusion criteria

- Any prior endocrine therapy for ABC
- Inflammatory breast cancer
- Active cardiac disease or history of cardiac dysfunction, including QTcF >450 msec
- CNS metastases
- Symptomatic visceral disease

- AI, aromatase inhibitor; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; NCCN, National Comprehensive Cancer Network; QTcF, Fridericia's corrected QT interval. Perimenopausal defined as neither premenopausal nor postmenopausal per NCCN guidelines. Goserelin included in all combinations.

Primary endpoint: PFS (investigator-assessed)



PFS (investigator assessment)	Ribociclib + tamoxifen/NSAI n=335	Placebo + tamoxifen/NSAI n=337
Number of events, n (%)	131 (39.1)	187 (55.5)
Median PFS, months (95% CI)	23.8 (19.2–NR)	13.0 (11.0–16.4)
Hazard ratio (95% CI)	**0.553 (0.441–0.694)**	
One-sided p value	**0.0000000983**	

No. at risk

Ribociclib + tamoxifen/NSAI	335	301	284	264	245	235	219	178	136	90	54	40	20	3	1	0
Placebo + tamoxifen/NSAI	337	273	248	230	207	183	165	124	94	62	31	24	13	3	1	0

- CI, confidence interval; NR, not reached.
  Goserelin included in all combinations.

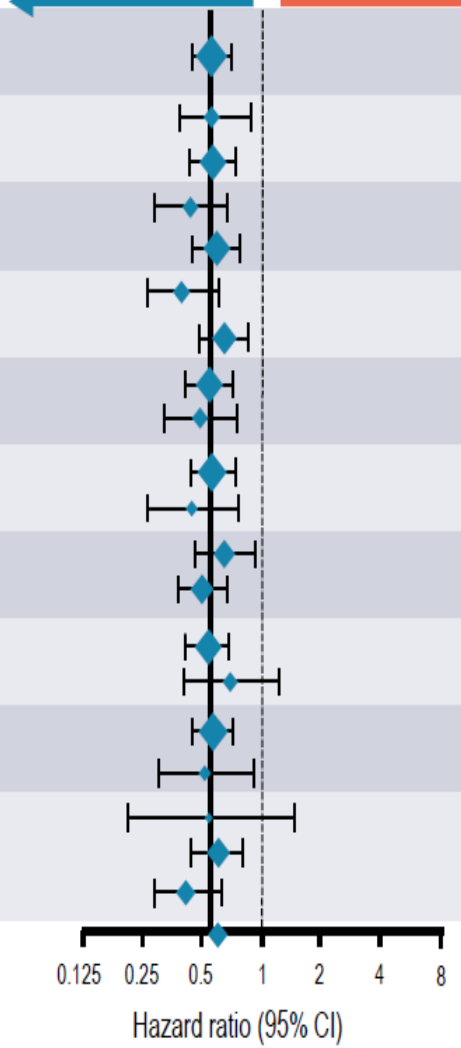
PFS by endocrine therapy partner (investigator-assessed)

PFS (investigator assessment)	Tamoxifen		NSAI	
	Ribociclib arm n=87	Placebo arm n=90	Ribociclib arm n=248	Placebo arm n=247
Number of events, n	39	55	92	132
Median PFS, months (95% CI)	22.1 (16.6–24.7)	11.0 (9.1–16.4)	27.5 (19.1–NR)	13.8 (12.6–17.4)
Hazard ratio (95% CI)	**0.585 (0.387–0.884)**		**0.569 (0.436–0.743)**	

- Goserelin included in all combinations.

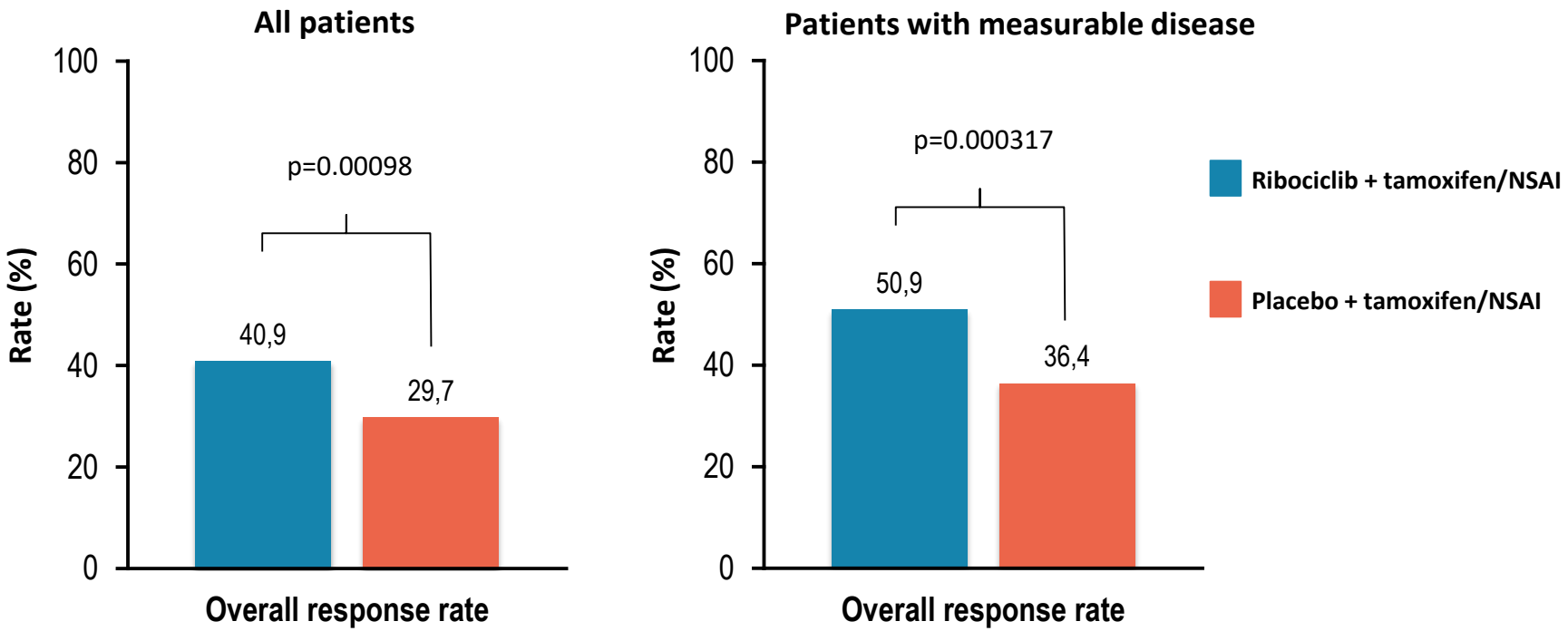
PFS subgroup analysis*

Subgroup		n (%)	Hazard ratio	95% CI
All patients		672 (100)	0.553	0.441–0.694
Endocrine therapy partner	Tamoxifen	177 (26)	0.585	0.387–0.884
	NSAI	495 (74)	0.569	0.436–0.743
Age	<40 years	186 (28)	0.443	0.293–0.671
	≥40 years	486 (72)	0.590	0.449–0.777
Race‡	Asian	198 (29)	0.401	0.258–0.625
	Non-Asian	413 (61)	0.657	0.492–0.877
ECOG performance status§	0	500 (74)	0.549	0.417–0.721
	≥1	166 (25)	0.495	0.320–0.765
ER/PgR status	ER+ and PgR+	572 (85)	0.574	0.446–0.739
	Other	100 (15)	0.444	0.258–0.765
Liver and/or lung involvement	No	329 (49)	0.642	0.454–0.907
	Yes	343 (51)	0.503	0.375–0.677
Bone-only disease	No	513 (76)	0.533	0.415–0.686
	Yes	159 (24)	0.703	0.414–1.194
Prior chemotherapy for advanced disease	No	578 (86)	0.566	0.443–0.724
	Yes	94 (14)	0.547	0.314–0.954
Disease-free interval	≤12 months	36 (5)	0.560	0.210–1.490
	>12 months	366 (54)	0.615	0.455–0.832
	De novo	270 (40)	0.428	0.287–0.640



ER, estrogen receptor; PgR, progesterone receptor.
*Locally assessed PFS; ‡Non-Asian race includes Caucasian, Black, and Native American;
§ ECOG performance status missing for n=6; 1 patient had an ECOG performance status of 2.

Secondary endpoints



- The CBR in patients with measurable disease was 79.9% for ribociclib + tamoxifen/NSAI vs 67.3% for placebo + tamoxifen/NSAI (p=0.000340)
- Overall survival data were immature at the cut-off date

- CBR, clinical benefit rate.

CBR = complete response + partial response + (stable disease + non-complete response/non-progressive disease ≥24 weeks).

- Goserelin included in all combinations.

"Classic" versus "New" algorithm for ER+/HER2– ABC

Sites and extent of disease & symptoms; PS; degree of HR expression; disease free & treatment-free intervals; prior adjuvant; patients' preference

No life-threatening disease, Hormone-responsive

1st line hormonal therapy (NSAI, Fulv, Exe+Eve)

median PFS 12-15 mo

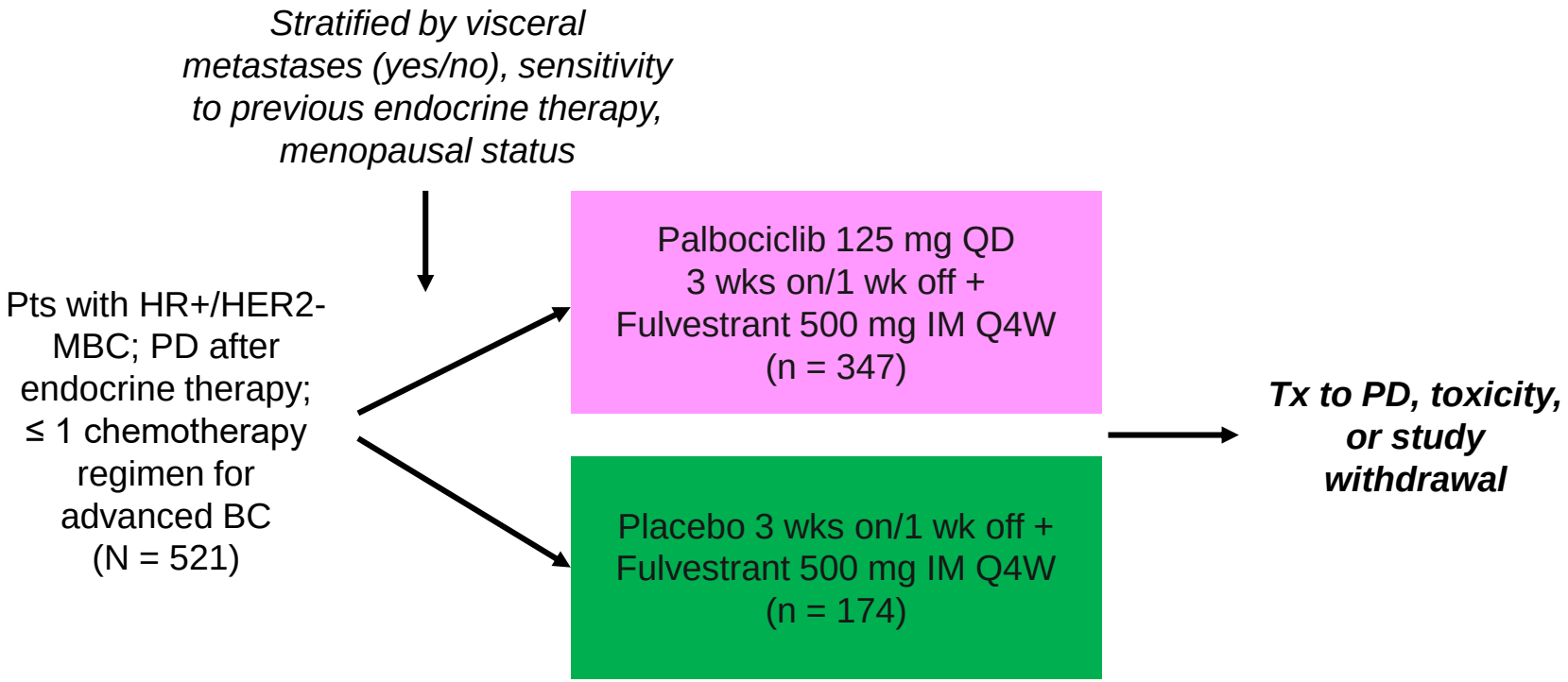
2nd line hormonal therapy (Exe+Eve, Fulv)

median PFS 4-9 mo

3rd line hormonal therapy (Tam, Megestrol)

	PALOMA 2		Monaleesa2		MONARCH 3		Monaleesa7 (pre/perimenop)	
	Let + Palbo	Let + Plac	Let + Ribo	Let + Plac	NSAI + Abema	NSAI + Plac	ET + Ribo	ET + Plac
Pts #	444	222	334	334	328	165	335	337
Median PFS mo.	24.8 (HR 0.58)	14.5	25.3 (HR 0.56)	16	NR (HR 0.54)	14.7	23.8 (HR 0.55)	13

PALOMA 3: A Phase III, Double-blind, Placebo-controlled Study of Palbociclib + Fulvestrant



- **Primary endpoint: investigator-assessed PFS**
- **Secondary endpoints: ORR, CBR (CR, PR, or SD for ≥ 24 wks), OS, pt-reported outcomes, safety**

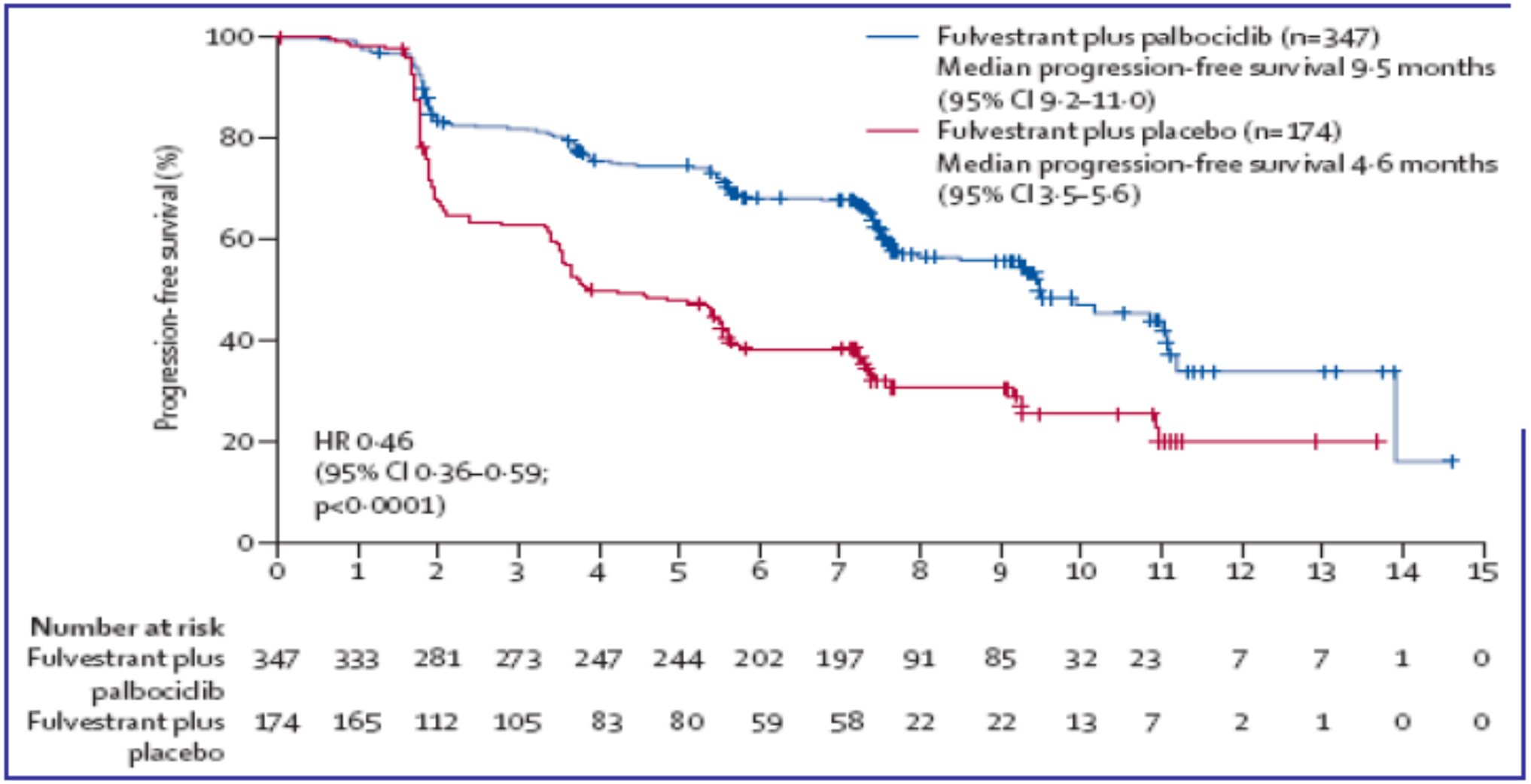
PALOMA 3

- **Baseline characteristics well balanced between arms; ~ 75% < 65 yrs of age**

Characteristic	Palbociclib + Fulvestrant (n = 347)	Placebo + Fulvestrant (n = 174)
Median age, yrs (range)	57 (30-88)	56 (29-80)
ER+ and PgR+, %	68.6	63.8
ER+ and PgR-, %	26.2	27.6
Sensitive to prior hormonal Tx, %	79.0	78.2
Metastatic disease at study entry, %	85.3	83.9
Prior AI ± GnRH agonist, %	68.6	67.8
Prior tamoxifen ± GnRH agonist, %	18.2	17.2
Prior neo/adjuvant chemotherapy, %	41.5	43.1
Prior lines of tx for metastatic disease, %		
▪ 1	38.0	40.2
▪ 2	25.9	24.7
▪ ≥ 3	11.8	9.2

Cristofanilli M, et al. SABCS 2015. Abstract P4-13-01.
Turner NC, et al. N Engl J Med. 2015;373:209-219.

PALOMA 3


Fulvestrant plus palbociclib (n=347)
Median progression-free survival 9·5 months
(95% CI 9·2–11·0)
Fulvestrant plus placebo (n=174)
Median progression-free survival 4·6 months
(95% CI 3·5–5·6)
HR 0·46
(95% CI 0·36–0·59;
p<0·0001)
Progression-free survival (%)
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Number at risk
Fulvestrant plus palbociclib 347 333 281 273 247 244 202 197 91 85 32 23 7 7 1 0
Fulvestrant plus placebo 174 165 112 105 83 80 59 58 22 22 13 7 2 1 0 0

PALOMA-3: PFS in Overall Population and Specific Pt Subgroups

- **Median follow-up: 8.9 mos**

Median PFS, Mos (95% CI)	Palbociclib + Fulvestrant (n = 345)	Placebo + Fulvestrant (n = 172)	HR (95% CI)	*P* Value
ITT population	9.5 (9.2-11.0)	4.6 (3.5-5.6)	0.45 (0.36-0.59)	< .0001
Pre-/perimenopausal pts	9.5 (7.4-NE)	5.6 (1.8-7.6)	0.50 (0.29-0.87)	.0065
Postmenopausal women	9.9 (8.5-11.0)	3.9 (3.5-5.5)	0.45 (0.34-0.59)	< .0001
No earlier systemic therapy for metastatic disease	9.5 (7.4-NE)	5.4 (2.1-10.9)	0.55 (0.32-0.92)	.0214
Disease responsive to earlier endocrine therapy	10.2 (9.4-11.2)	4.2 (3.5-5.6)	0.42 (0.32-0.56)	< .0001
AIs as most recent therapy	9.5 (9.2-11.0)	3.7 (3.4-5.5)	0.42 (0.31-0.56)	< .0001

Cristofanilli M, et al. SABCS 2015. Abstract P4-13-01.

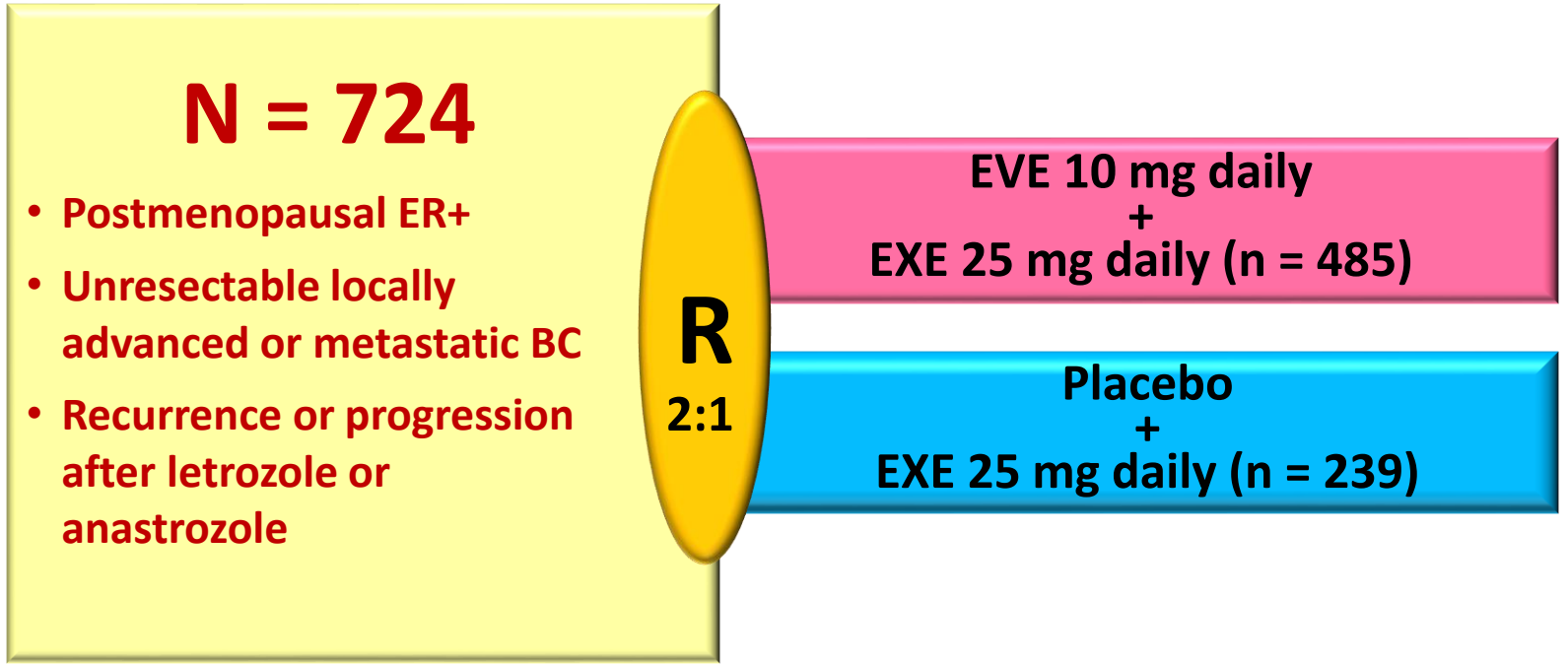
PALOMA 3: response and clinical benefit rates

- **Median follow-up: 8.9 mos**

Outcome, % (95% CI)	Palbociclib + Fulvestrant (n = 345)	Placebo + Fulvestrant (n = 172)	Odds Ratio (95% CI)	*P* Value
ITT population				
▪ ORR	19.0 (15.0-23.6)	8.6 (4.9-13.8)	2.47 (1.36-4.91)	.0019
▪ CBR	66.6 (61.3-71.5)	39.7 (32.3-47.3)	3.05 (2.07-4.61)	< .0001
Pts with measurable disease at BL				
▪ ORR	24.6 (19.6-30.2)	10.9 (6.2-17.3)	2.69 (1.43-5.26)	.0012
▪ CBR	NR	NR	3.10 (1.99-4.92)	< .0001

Cristofanilli M, et al. SABCS 2015. Abstract P4-13-01.

BOLERO-2 (Ph III): Everolimus in Advanced BC



Endpoints

- **Primary:** PFS (local assessment)
- **Secondary:** OS, ORR, QOL, safety, bone markers, PK

Abbreviations: BC, breast cancer; ER+, estrogen receptor-positive; EVE, everolimus; EXE, exemestane; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Ph, phase; PK, pharmacokinetics; QOL, quality of life.

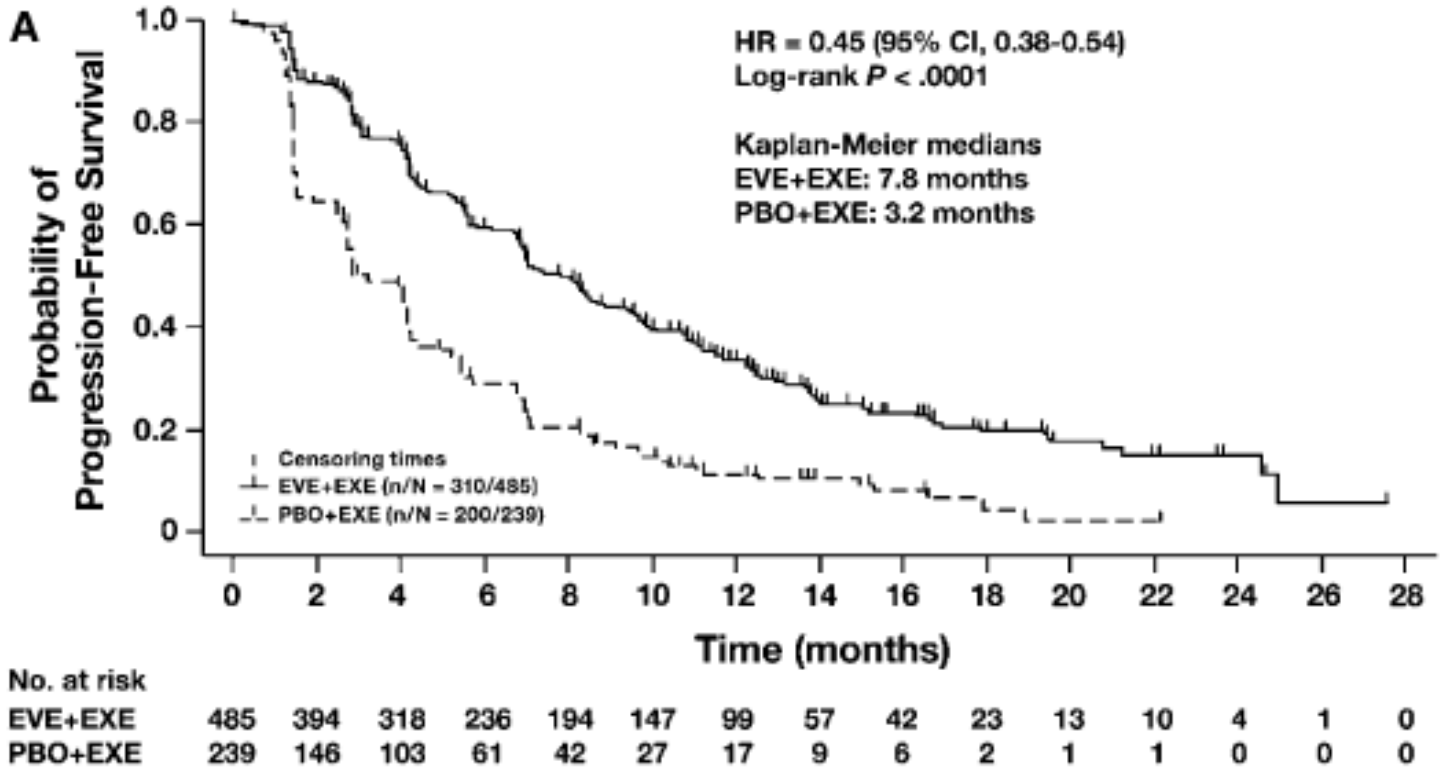
•**Baselga J, et al. *N Engl J Med*. 2012;366(6):520-529;** ClinicalTrials .gov number, NCT00863655.)

BOLERO-2: Baseline Characteristics Were Generally Balanced Between Arms

Characteristic	Everolimus + Exemestane (N=485), %	Placebo + Exemestane (N=239), %
Median age (range), years	62 (34, 93)	61 (28, 90)
Race		
Caucasian	74	78
Asian	20	19
Performance status 0	60	59
Liver involvement	33	30
Lung involvement	29	33
Measurable disease[a]	70	68

Adapted from: Baselga J, et al. *N Engl J Med*. 2012;366(6):520-529.

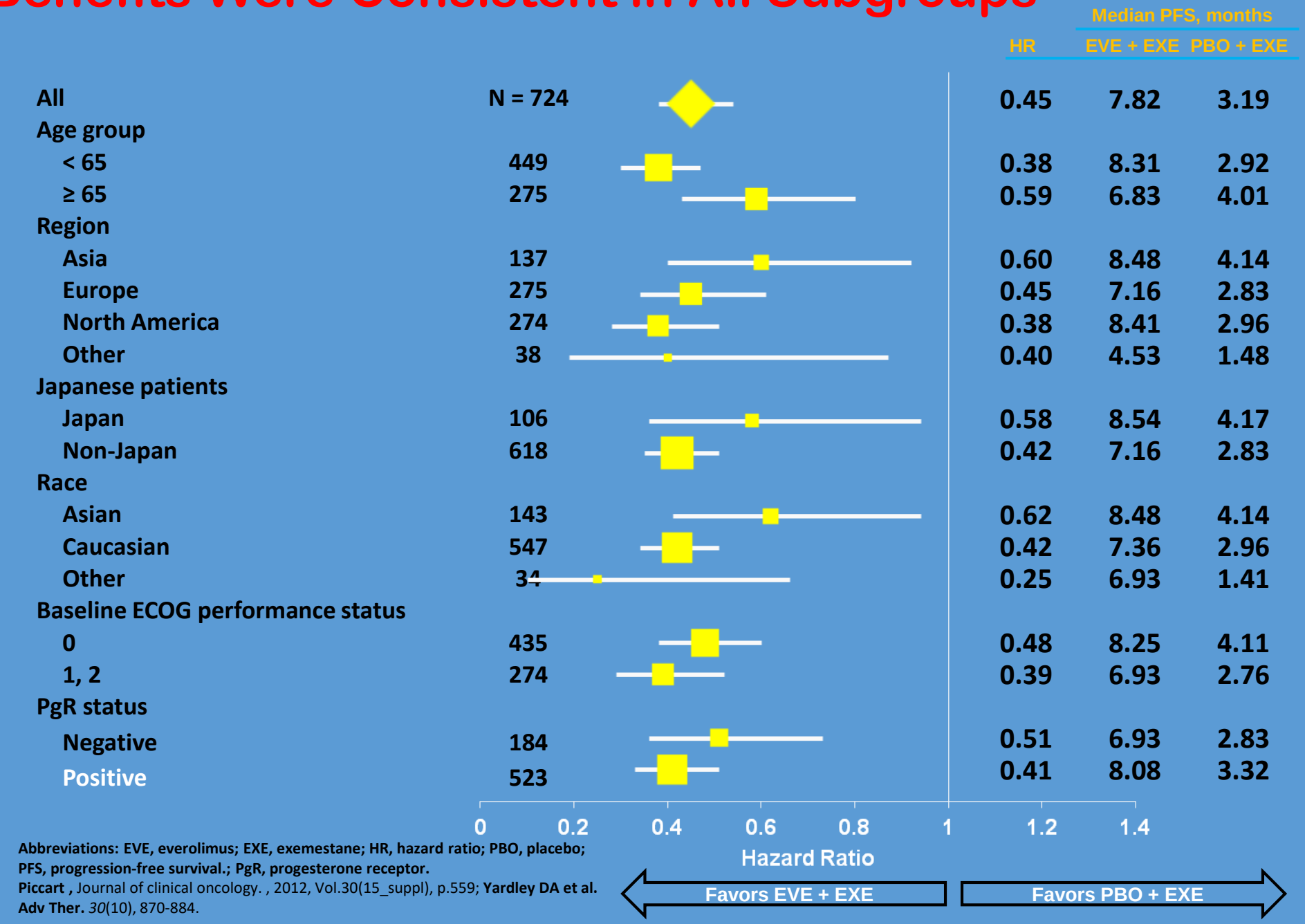
PFS Based on Local Assessment at 18-mo Follow-up in BOLERO-2 Confirms Earlier Reports



Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo.

Piccart , Journal of clinical oncology. , 2012, Vol.30(15_suppl), p.559; **Yardley DA et al. Adv Ther.** *30*(10), 870-884.

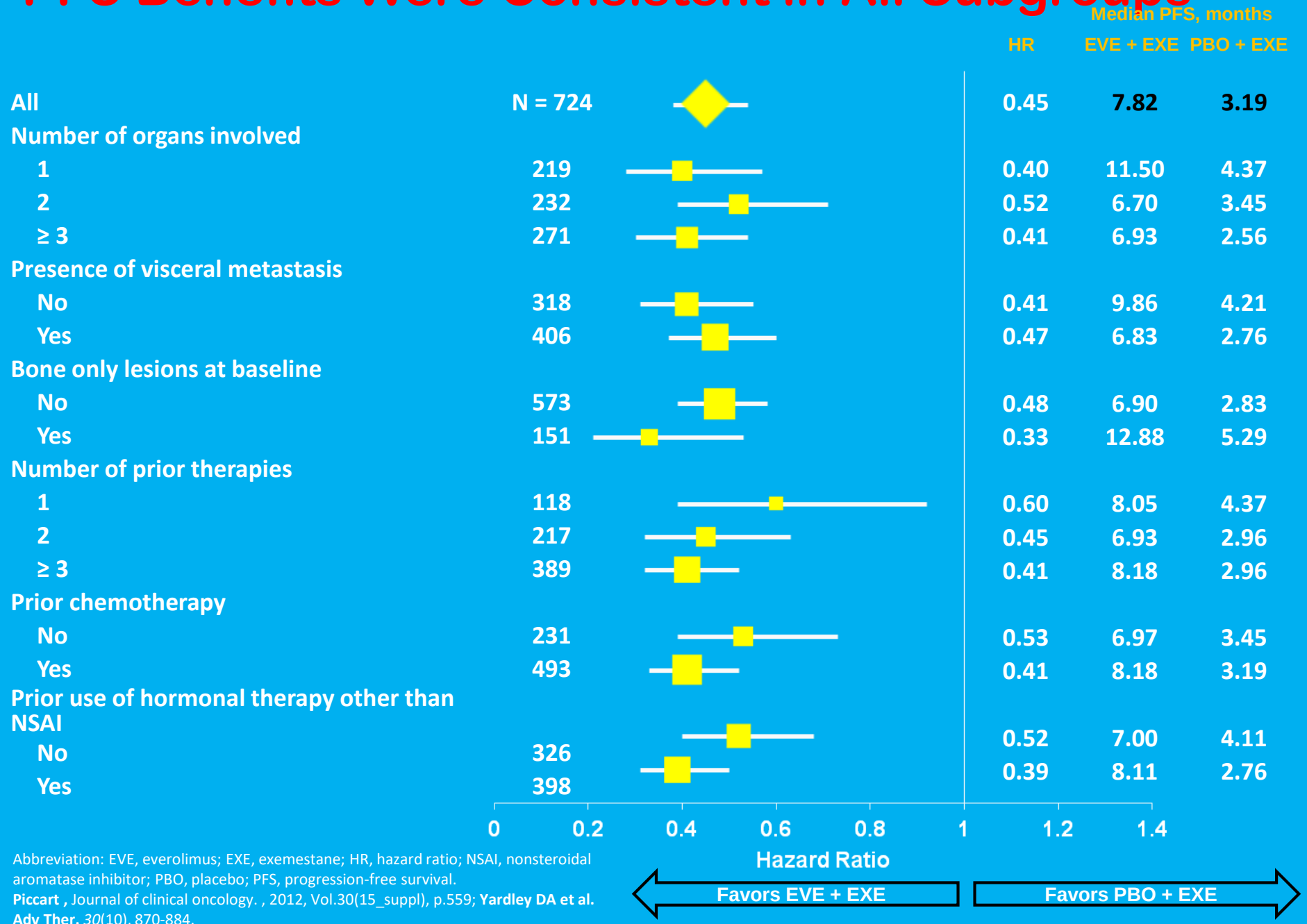
PFS Benefits Were Consistent in All Subgroups



Abbreviations: EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo; PFS, progression-free survival.; PgR, progesterone receptor.

Piccart , Journal of clinical oncology. , 2012, Vol.30(15_suppl), p.559; **Yardley DA et al. Adv Ther.** *30*(10), 870-884.

PFS Benefits Were Consistent in All Subgroups



Abbreviation: EVE, everolimus; EXE, exemestane; HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; PBO, placebo; PFS, progression-free survival.

Piccart , Journal of clinical oncology. , 2012, Vol.30(15_suppl), p.559; **Yardley DA et al. Adv Ther.** *30*(10), 870-884.

BOLERO-2 (18 mo f/up): Common Adverse Events Were Consistent With the Established Safety Profile of Everolimus

	Everolimus + Exemestane (N=482), %					Placebo + Exemestane (N=238), %				
		Grade					Grade			
	All	1	2	3	4	All	1	2	3	4
Total	100	7	40	44	9	91	26	36	23	5
Stomatitis	59	29	22	8	0	12	9	2	<1	0
Rash	39	29	9	1	0	7	5	2	0	0
Fatigue	37	18	14	4	<1	27	16	10	1	0
Diarrhea	34	26	6	2	<1	19	14	4	<1	0
Nausea	31	21	9	<1	<1	29	21	7	1	0
Appetite decreased	31	19	10	1	0	13	8	4	1	0
Non-infectious pneumonitis*	16	7	6	3	0	0	0	0	0	0
Hyperglycemia*	14	4	5	5	<1	2	1	1	<1	0

Annals of Oncology

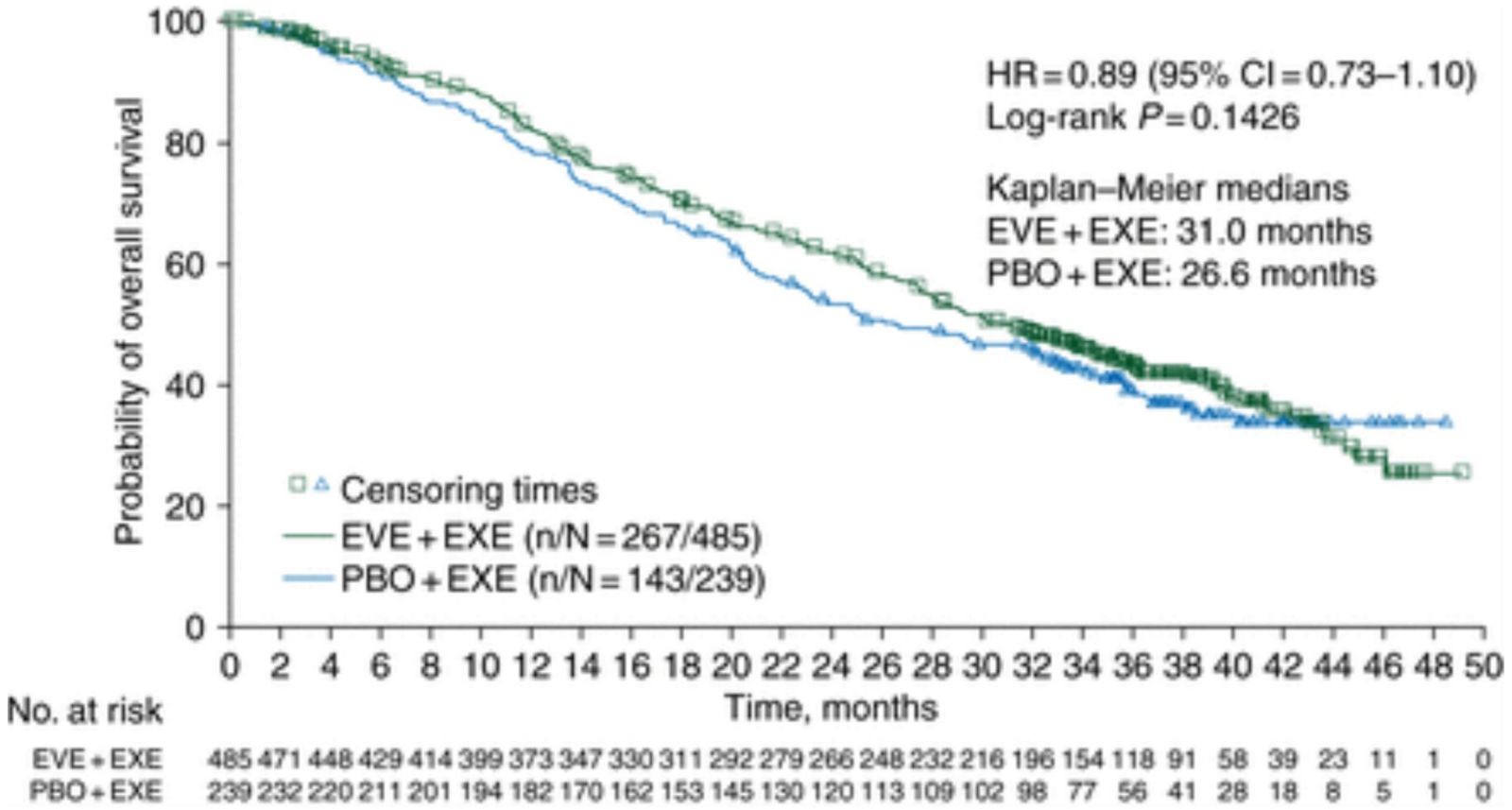
original articles

Annals of Oncology 25: 2357–2362, 2014
doi: 10.1093/annonc/mdu456
Published online 17 September 2014

Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2†

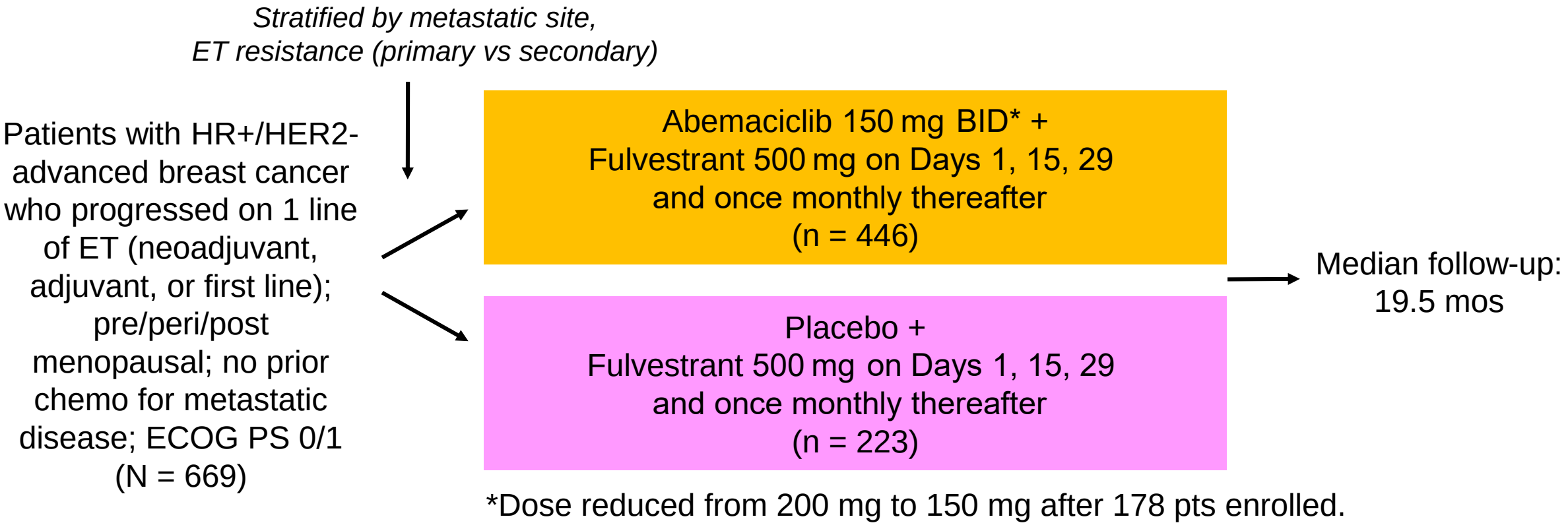
M. Piccart[1*], G. N. Hortobagyi[2], M. Campone[3], K. I. Pritchard[4], F. Lebrun[1], Y. Ito[5], S. Noguchi[6], A. Perez[7], H. S. Rugo[8], I. Deleu[9], H. A. Burris III[10], L. Provencher[11], P. Neven[12], M. Gnant[13], M. Shtivelband[14], C. Wu[15], J. Fan[15], W. Feng[15], T. Taran[15] & J. Baselga[16]

BOLERO-2 (39-mo): Final OS Analysis



- At 39 months' median follow-up, 410 deaths had occurred (data cutoff date: 03 October 2013)
  - 55% deaths (n = 267) in the EVE+EXE arm vs 60% deaths (n = 143) in the PBO+EXE arm

MONARCH 2: DISEGNO DELLO STUDIO



*Dose reduced from 200 mg to 150 mg after 178 pts enrolled.

- Pts enrolled at 142 centers in 19 countries
- Primary endpoint: PFS (investigator assessed)
- Secondary endpoints: OS, ORR, clinical benefit rate, safety

Sledge GW, et al. ASCO 2017. Abstract 1000.

Sledge GW, et al. ASCO 2017. Abstract 1000.

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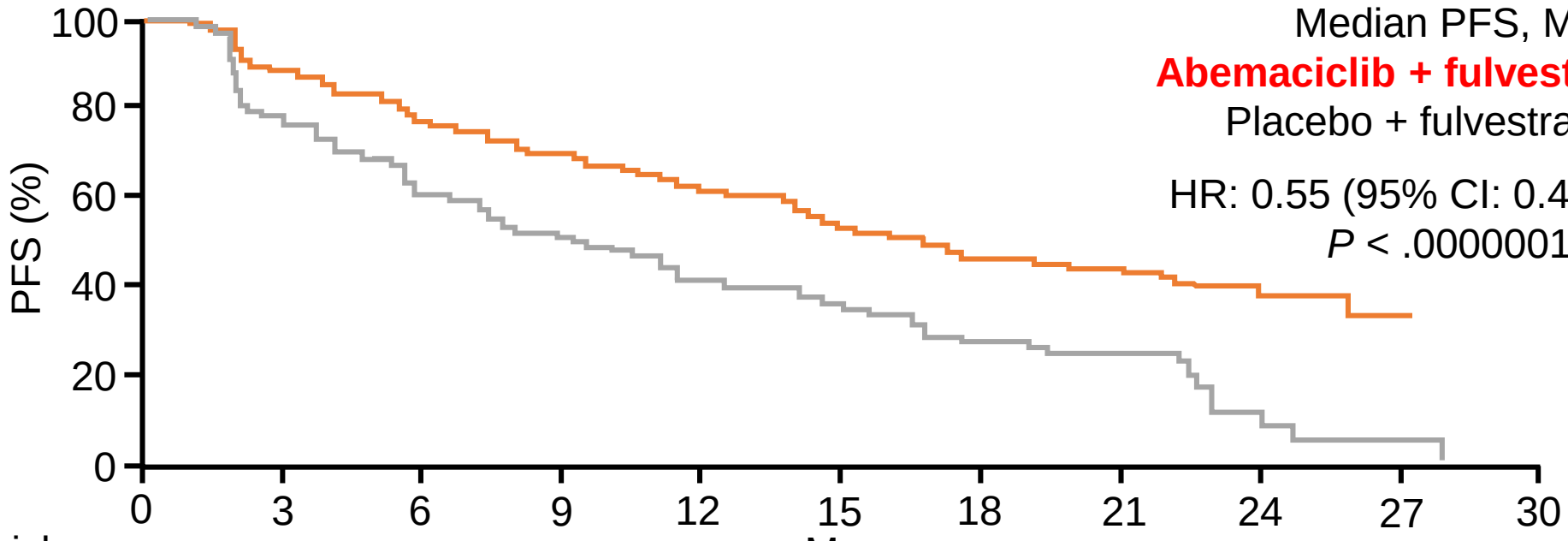
MONARCH 2: CARATTERISTICHE DEI PAZIENTI

Characteristic	Abemaciclib + Fulvestrant (n = 446)	Placebo + Fulvestrant (n = 223)
Median age, yrs (range)	59 (32-91)	62 (32-87)
Primary ET resistance, %	25	26
Most recent ET, % ▪ Neoadjuvant/adjuvant ▪ Metastatic	 59 38	 60 38
Prior aromatase inhibitor, %	71	67
PgR positive, %	76	77
Metastatic site, % ▪ Visceral ▪ Bone only ▪ Other (nonvisceral soft tissue)	 55 28 17	 57 26 17
Measureable disease, %	71	74
Postmenopausal, %	83	81

Sledge GW, et al. ASCO 2017. Abstract 1000.

MONARCH 2: PFS



Patients at risk:											
Abemaciclib	446	367	314	281	234	171	101	65	32	2	0
Placebo	223	165	123	103	80	61	32	13	4	1	0

- PFS benefit with addition of abemaciclib to fulvestrant observed across all pt subgroups, except those with nonvisceral soft tissue metastases
- ORR, abemaciclib cohort vs placebo cohort: 35.2% vs 16.1%

Sledge GW, et al. ASCO 2017. Abstract 1000. Reproduced with permission.

MONARCH 2: EFFETTI COLLATERALI

Treatment- Emergent AE Occurring in ≥ 20% in Either Arm, %	Abemaciclib + Fulvestrant (n = 441)		Placebo + Fulvestrant (n = 223)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any	98.6	60.5	89.2	22.8
Diarrhea*	86.4	13.4	24.7	0.4
Neutropenia	46.0	26.5	4.0	1.7
Nausea	45.1	2.7	22.9	0.9
Fatigue	39.9	2.7	26.9	0.4
Abdominal pain	35.4	2.5	15.7	0.9
Anemia	29.0	7.2	3.6	0.9
Leukopenia	28.3	8.8	1.8	0
Decreased appetite	26.5	1.1	12.1	0.4
Vomiting	25.9	0.9	10.3	1.8
Headache	20.2	0.7	15.2	0.4

*Incidence of diarrhea greatly reduced after starting abemaciclib dose amended from 200 mg to 150 mg.

Sledge GW, et al. ASCO 2017. Abstract 1000

"Classic" versus "New" algorithm for ER+/HER2– ABC

Sites and extent of disease & symptoms; PS; degree of HR expression; disease free & treatment-free intervals; prior adjuvant; patients' preference

No life-threatening disease, Hormone-responsive

↓

1st line hormonal therapy (NSAI, Fulv, Exe+Eve)

↓

median PFS 12-15 mo

↓

2ndline hormonal therapy (Exe+Eve, Fulv)

↓

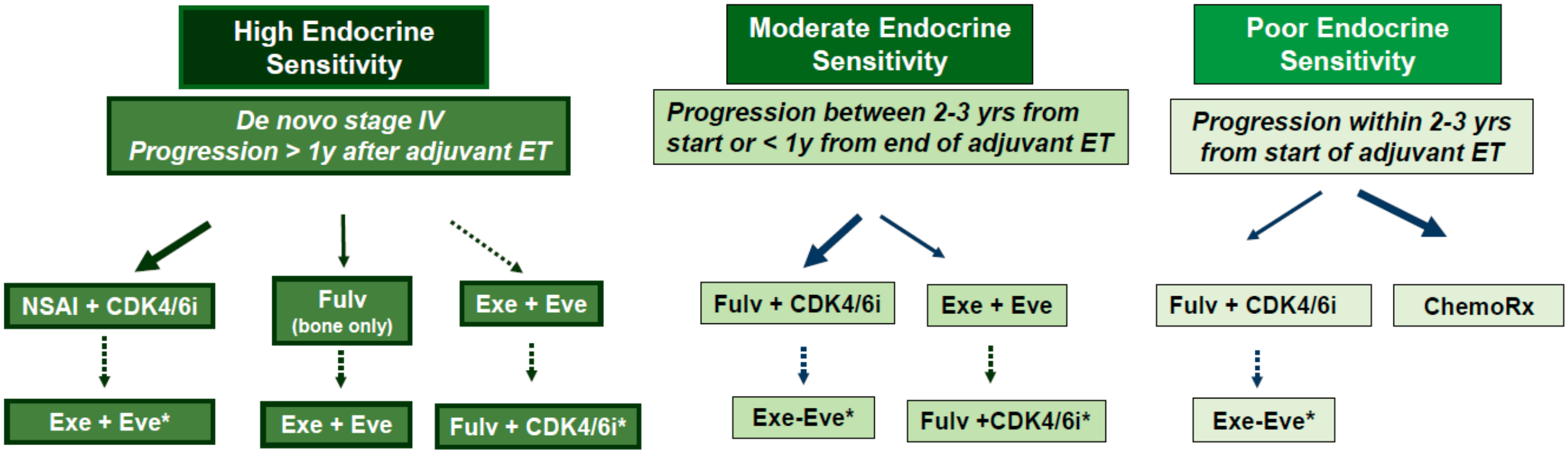
median PFS 4-9 mo

↓

3rdline hormonal therapy (Tam, Megestrol)

	BOLERO 2		PALOMA 3		MONARCH 2	
	Exe + Eve	Exe +Plac	Fulv + Palbo	Fulv + Plac	Fulv+ Abema	Fulv+Plac
Pts #	485	239	347	174	446	223
Median PFS mo.	6.9 (HR 0.43)	2.8	9.2 (HR 0.42)	3.8	16.4 (HR 0.55)	9.3

HR+HER2- ABC: Changing paradigms (work still in progress....)



* These sequences are not supported by data from clinical trials

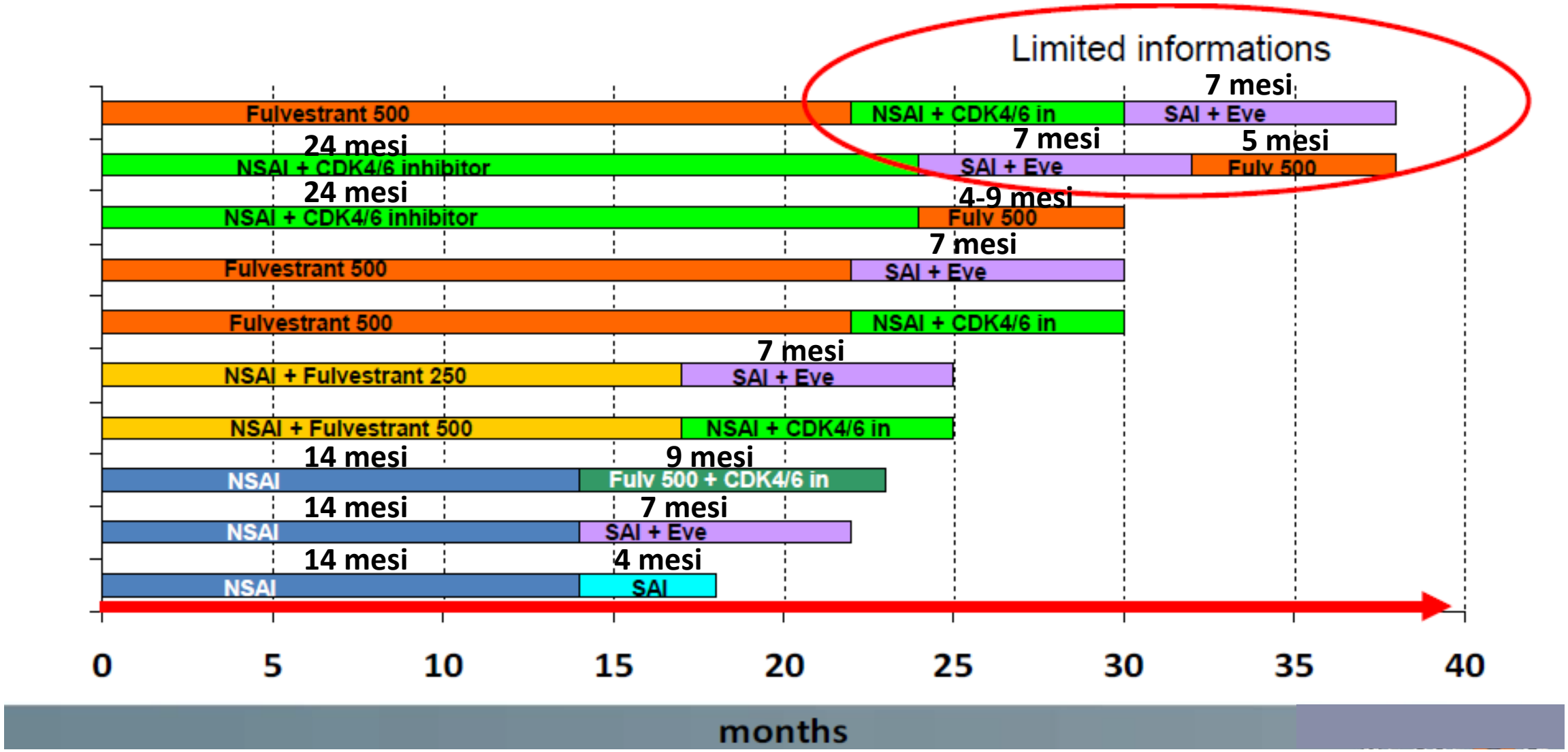
INIBITORI CDK4-6 + OT O SOLO OT? PRO E CONTRO

- **CDK4/6 inhibitor first**
  - Higher probability of response
  - Higher probability to delay progression
  - Higher probability of side effects
  - Carefull consideration of drug interaction
  - More frequent access to hospital
  - Limited information on efficacy of treatment after failing CDK4/in.

- **Hormone alone first**
  - Good probability of effect
  - Good probability of compliance to treatment
  - Lessfrequent access to hospital
  - Reduced hospital work-load
  - Use of CDK4/6in. at progression not always allowed by NHS rules
  - Limited information on efficacy of CDK4/6in. if added to fulvestrant or with AI at PD

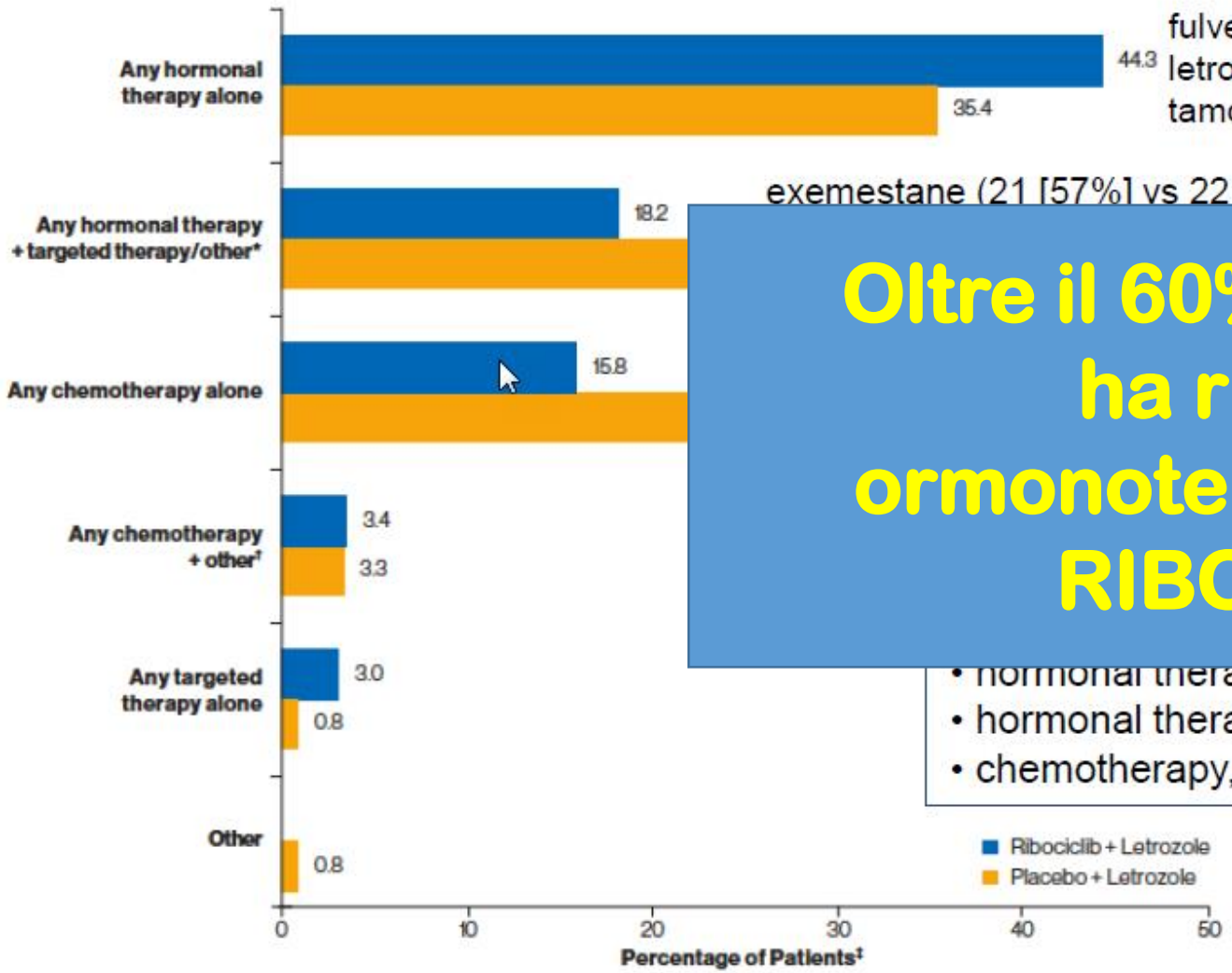
The best use of available options in sequence might be rationale?

EFFETTO CUMULATIVO DELLE OPZIONI TERAPEUTICHE DISPONIBILI SU PFS



Opzioni di trattamento a progressione da inibitori di cicline

First Subsequent Therapies Following Discontinuation from MONALEESA-2



fulvestrant (40 [45%] vs 53 [62%]), letrozole (32 [36%] vs 18 [21%]), tamoxifen (8 [9%] vs 10 [12%]).

Median time to hormonal therapy 25.0 vs 22.6 months

exemestane (21 [57%] vs 22 [38%]).

Median time to hormonal therapy + targeted ... 33.0 months

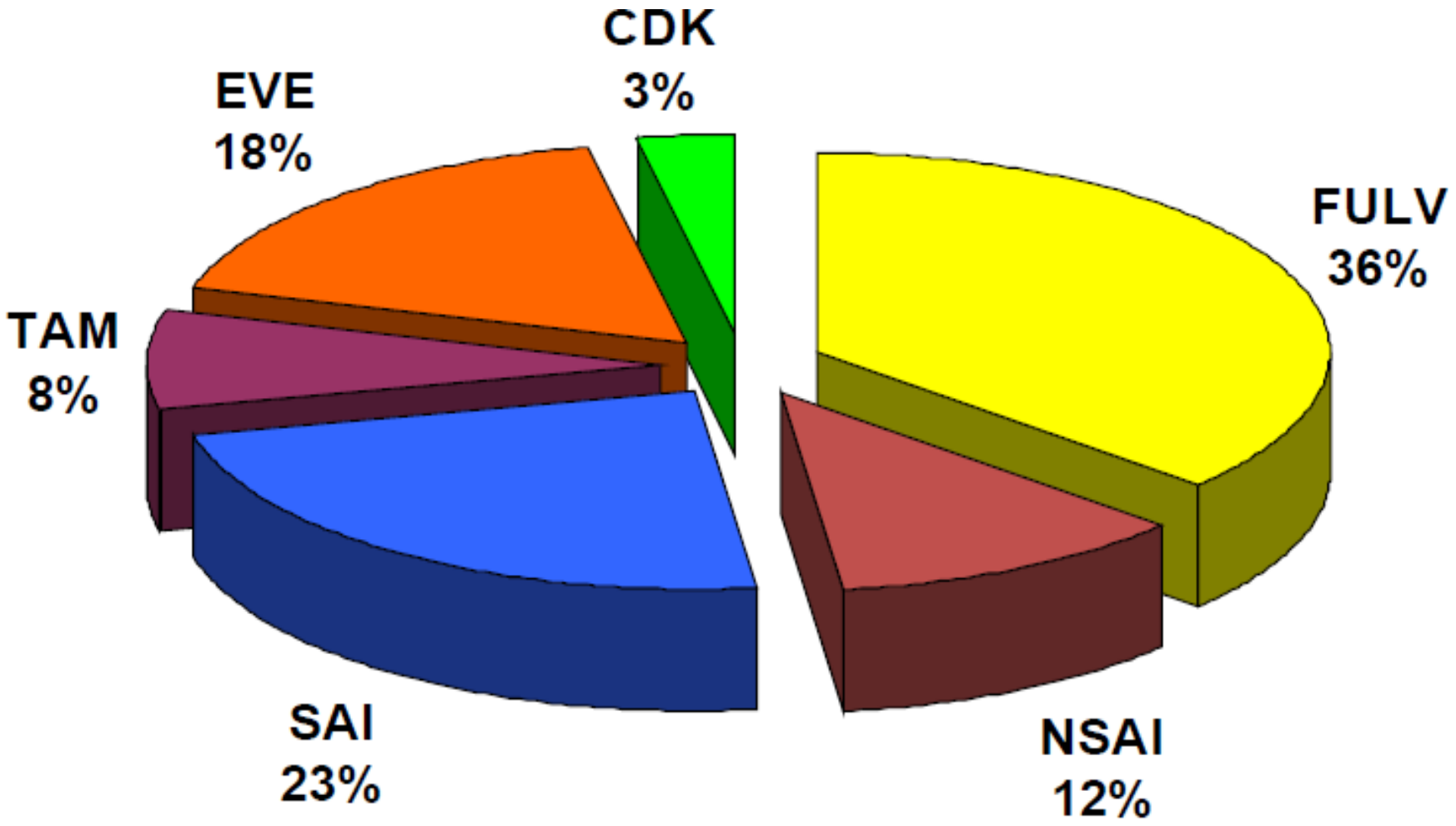
...erapy was NR vs

Oltre il 60% dei pazienti ha ricevuto ormonoterapia dopo IL RIBOCICLIB

- hormonal therapy 34/90 [38%] vs 30/87 [35%].
- hormonal therapy + targeted therapy/other 13/37 [**35**%] vs 28/58 [**48**%]
- chemotherapy, 11/32n[**34**%] vs 20/55 [**36**%]

*Includes patients who received hormonal therapy + targeted therapy + other;
†Includes patients who received chemotherapy + hormonal therapy;
‡Percentage is based on the number of patients who discontinued study treatment.
Data cut-off: January 2, 2017.

TRTTAMENTI DOPO FALLIMENTO DELLA PRIMA LINEA CON CDK4/6



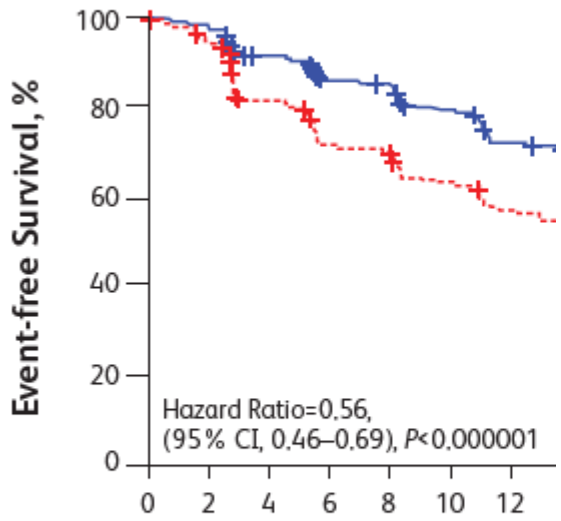
From: Blakwell SABCS 2017; Rugo ESMO 2017

Palbociclib Plus Letrozole as First-Line Therapy in Estrogen Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: Efficacy and Safety Updates With Longer Follow-Up Across Patient Subgroups

Hope S. Rugo,[1] Richard S. Finn,[2] Véronique Diéras,[3,4] Johannes Ettl,[5] Oleg Lipatov,[6] Anil A. Joy,[7] Nadia Harbeck,[8] Aurelio Castrellon,[9] Dongrui R. Lu,[10] Ave Mori,[11] Eric R. Gauthier,[12] Cynthia Huang Bartlett,[13] Karen A. Gelmon,[14] Dennis J. Slamon[2]

[1]University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [2]David Geffen School of Medicine at UCLA, Santa Monica, CA, USA; [3]Institut Curie, Paris, France; [4]Centre Eugène Marquis, Rennes, France; [5]Rosenklinik and Poliklinik Klinikum rechts der Isar, Technische Universität München, Munich, Germany; [6]Republican Clinical Oncology Dispensary, Ufa, Russia; [7]Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada; [8]Brustzentrum der Universität München (LMU), München, Germany; [9]Memorial Cancer Institute, Breast Cancer Center, Pembroke Pines, FL, USA; [10]Pfizer Inc, La Jolla, CA, USA; [11]Pfizer S.r.l., Milan, Italy; [12]Pfizer Inc, San Francisco, CA, USA; [13]Pfizer Inc, Collegeville, PA, USA; [14]British Columbia Cancer Agency, Vancouver, BC, Canada

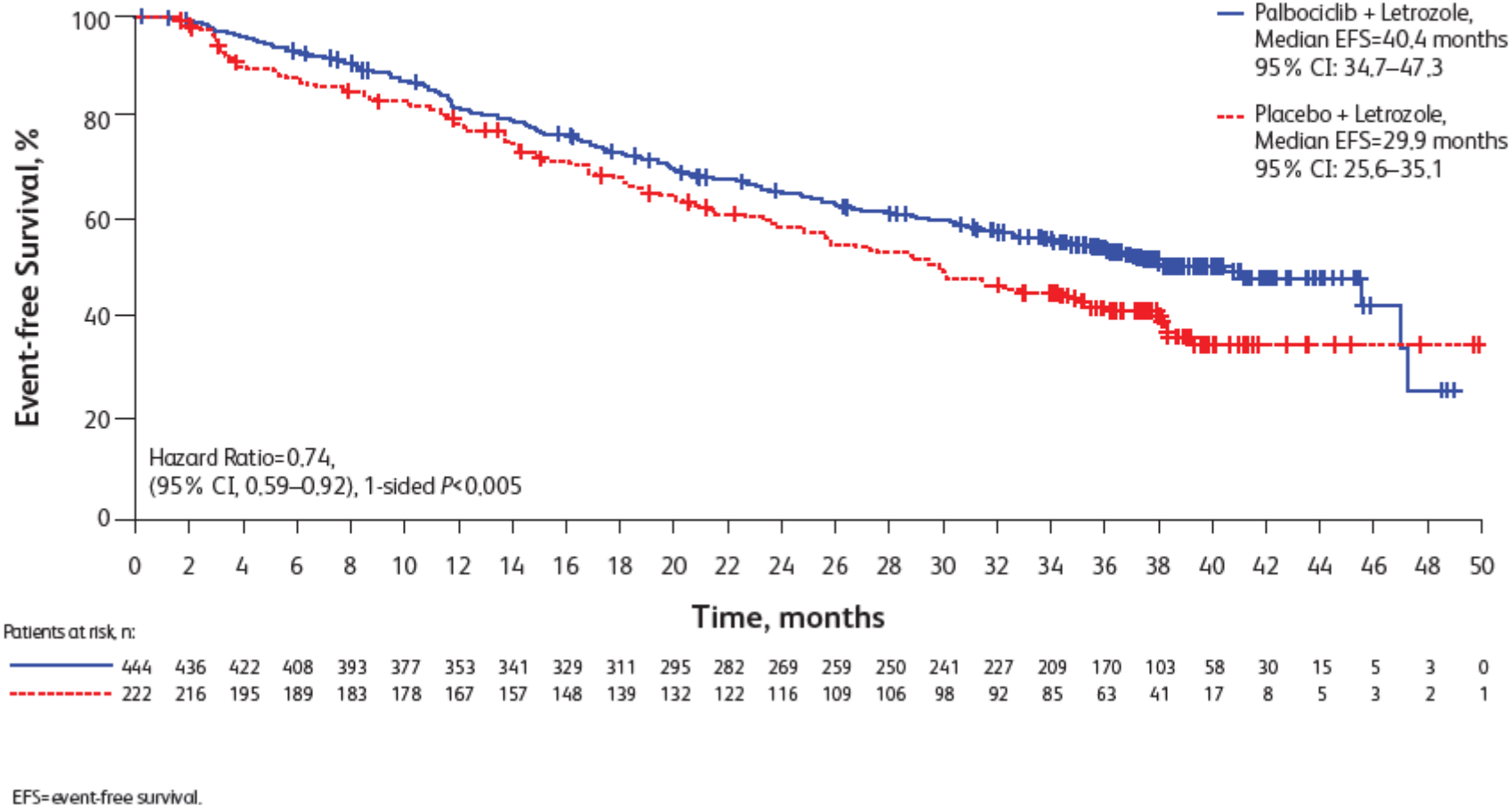
Figure 1. PFS (Investigator Assessed, ITT Population)



ITT=intent to treat; PFS=progression-free survival.

- Palbociclib plus letrozole delayed the time to subsequent chemotherapy by 10.5 months **(Figure 4)**.

Figure 4. Time to First Subsequent Chemotherapy



EFS=event-free survival.

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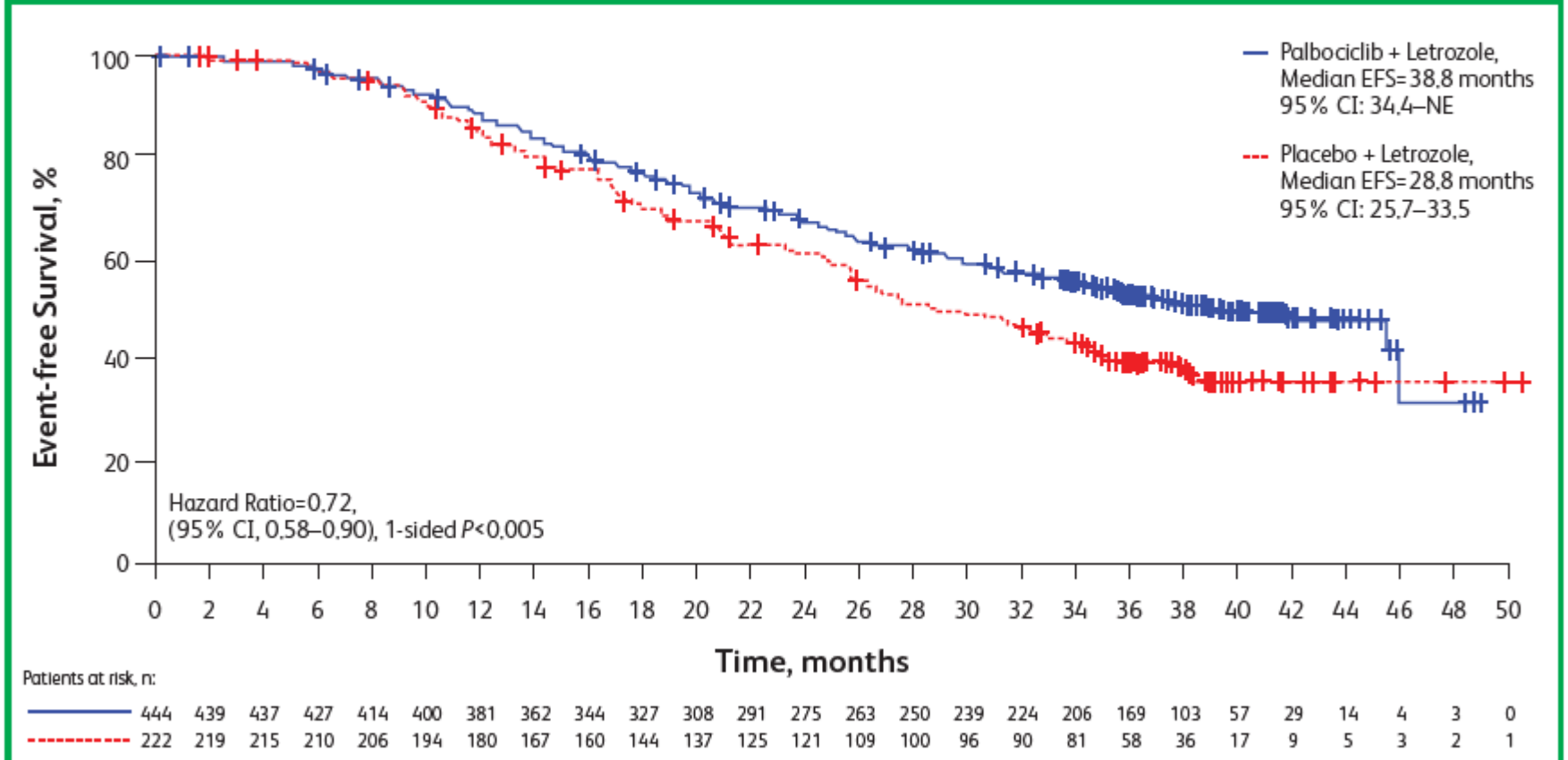
Subsequent Antic

- Among patients who r
  antihormonal therapy
  or exemestane was re
  respectively, and 13.7%

- The 10-month difference of PFS benefit from palbociclib, observed in the primary PFS analysis, was preserved, suggesting that the treatment benefit of the subsequent therapies was not compromised by palbociclib plus letrozole **(Figure 5)**.

Figure 5. Time to Second Subsequent Systemic Anticancer Therapy



EFS=event-free survival; NE=not estimable.

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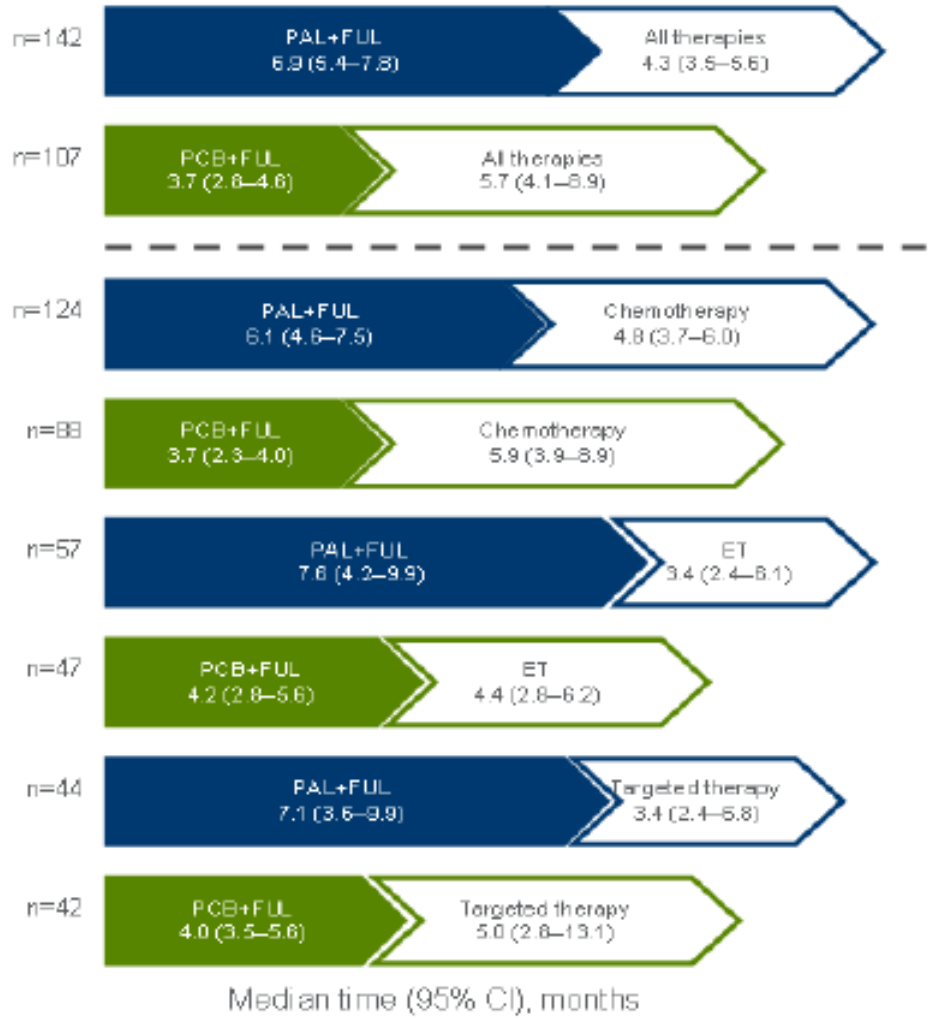
CONCLUSIONS

- This is the longest follow-up of a phase 3 study evaluating a CDK4/6 inhibitor in patients with metastatic breast cancer who had not received prior systemic therapy for advanced disease.
- After ~37 months of follow-up, palbociclib plus letrozole consistently improved median PFS vs placebo plus letrozole in the overall population (27.6 vs 14.5 months; **Figure 1**) and across patient subgroups (**Figure 2**). The safety profile remained consistent with previous observations.[5]
- Patients with a low disease burden or a demonstrated sensitivity to endocrine therapy alone derived substantial PFS benefit from palbociclib plus letrozole (>3 years median PFS); these findings were confirmed by a STEPP analysis of DFI.
- The improvement in PFS observed with palbociclib plus letrozole combination therapy in the first-line setting delayed the initiation of first subsequent anticancer therapy and the benefit of the therapy was not compromised.
- Similarly, palbociclib plus letrozole therapy delayed the initiation of first subsequent chemotherapy.
- Collectively, these data confirm that palbociclib plus letrozole should be regarded as an important first-line therapy option for patients with HR+/HER2– ABC.

Influence of palbocilcib + fulvestrant on the effect of subsequent treatments



Kaplan-Meier estimates of treatment durations for patients on post-study therapy for disease progression

Turner, SABCS 2016

Key Phase 3 Combination Trials in ER+ MBC

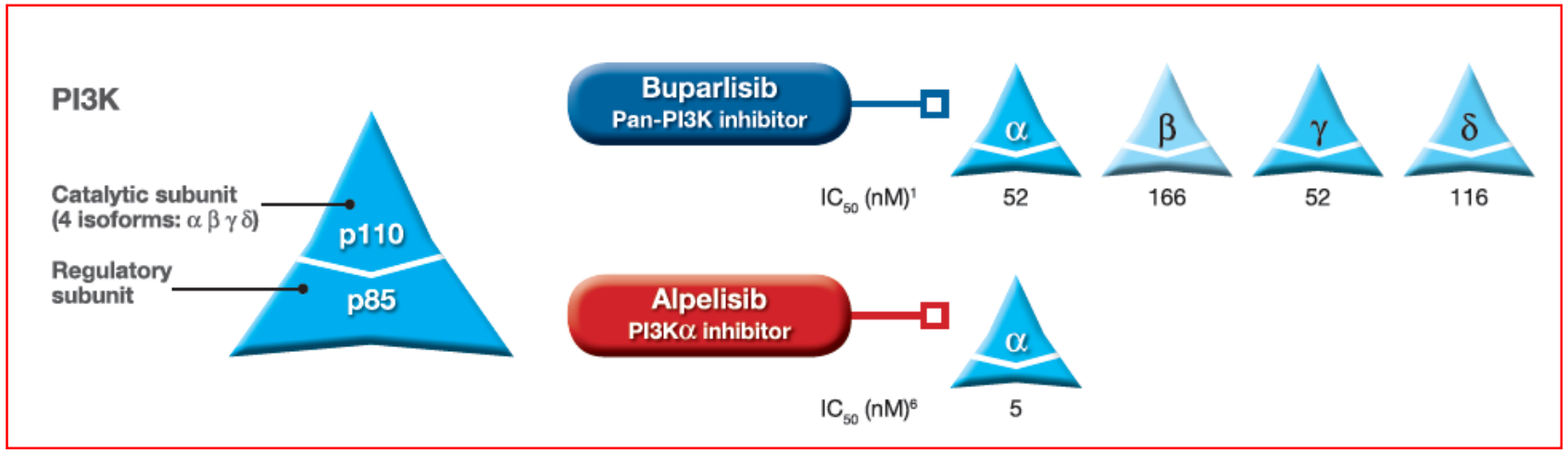
Agent	MoA	Phase 3 study	Comparator	Setting
Palbociclib (Pfizer)	CDK4/6	PALOMA 3	Fulvestrant	Post AI/antiestrogen
Palbociclib (Pfizer)	CDK4/6	PALOMA 2	Letrozole	1st Line
Ribociclib (Novartis)	CDK4/6	MONALEESA 2	Letrozole	1st Line
Abemaciclib (Eli Lilly)	CDK4/6	MONARCH 3	Letrozole	1st Line
Abemaciclib (Eli Lilly)	CDK4/6	MONARCH 2	Fulvestrant	Post AI/antiestrogen
Ribociclib (Novartis)	CDK4/6	MONALEESA 3	Fulvestrant	Post AI/antiestrogen
Ribociclib (Novartis)	CDK4/6	MONALEESA 7	Goserelin + ET	Pre-menopasue, 1st line
Buparlisib (Novartis)	Pan-PI3K	BELLE-2	Fulvestrant	Post AI
Buparlisib (Novartis)	Pan-PI3K	BELLE-3	Fulvestrant	Post AI + Everolimus
Alpelisib (Novartis)	PI3K α	SOLAR-1	Fulvestrant	Post AI
Taselisib (Roche)	PI3K α	SANDPIPER	Fulvestrant	Post AI
Entinostat (Syndax)	HDAC	E2112	Exemestane	Post NSAI, fulv, CDK4/6, everolimus

Key Phase 3 Combination Trials in ER+ MBC

Agent	MoA	Phase 3 study	Comparator	Setting
Palbociclib (Pfizer)	CDK4/6	PALOMA 3	Fulvestrant	Positive
Palbociclib (Pfizer)	CDK4/6	PALOMA 2	Letrozole	Positive
Ribociclib (Novartis)	CDK4/6	MONALEESA 2	Letrozole	Positive
Abemaciclib (Eli Lilly)	CDK4/6	MONARCH 3	Letrozole	Positive
Abemaciclib (Eli Lilly)	CDK4/6	MONARCH 2	Fulvestrant	Positive
Ribociclib (Novartis)	CDK4/6	MONALEESA 3	Fulvestrant	Post AI/antiestrogen
Ribociclib (Novartis)	CDK4/6	MONALEESA 7	Goserelin + ET	Positive
Buparlisib (Novartis)	Pan-PI3K	BELLE-2	Fulvestrant	Positive
Buparlisib (Novartis)	Pan-PI3K	BELLE-3	Fulvestrant	Positive
Alpelisib (Novartis)	PI3K α	SOLAR-1	Fulvestrant	Post AI
Taselisib (Roche)	PI3K α	SANDPIPER	Fulvestrant	Post AI
Entinostat (Syndax)	HDAC	E2112	Exemestane	Post NSAI, fulv, CDK4/6, everolimus

PI3K Inhibitors in Clinical Development

- **Buparlisib (BKM120)** is an oral pan-PI3K inhibitor targeting all four isoforms of class I PI3K (α, β, γ, δ)[1]
  - Targeting all class I isoforms may ensure broad activity in tumors with a range of molecular drivers[2–5]
- **Alpelisib (BYL719)** is an oral inhibitor selectively targeting the α isoform of class I PI3K
  - Inhibition of the α isoform may reduce off-target toxicity[5]

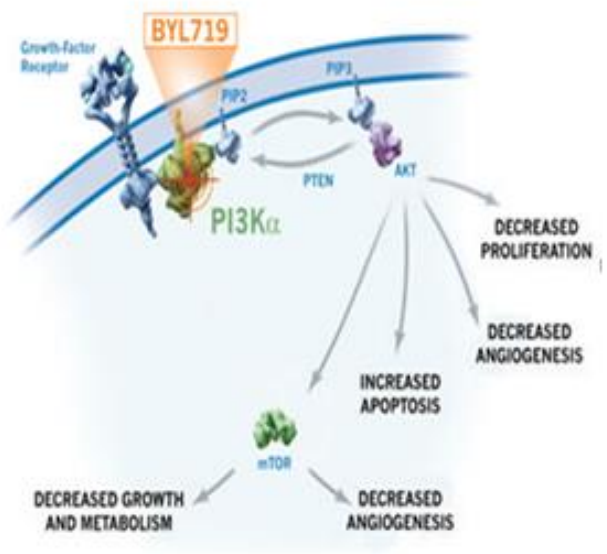


PI3K, phosphatidylinositol 3-kinase.

1. Maira SM, *et al. Mol Cancer Ther* 2012;11:317–328; 2. Liu P, *et al. Nat Rev Drug Discov* 2009;8:627–644;
3. Kang S, *et al. Proc Natl Acad Sci USA* 2006;103:1289–1294; 4. Hernandez-Aya LF, *et al. Oncologist* 2011;16:404–414;
5. Jia S, *et al. Curr Opin Cell Biol* 2009;21:199–208;

Alpelisib: A PI3Kα Selective Inhibitor

- Alpelisib is an oral inhibitor that selectively targets the α-isoform of class I PI3K
- Alpelisib does not cross the blood-brain barrier, potentially sparing any CNS adverse events
- PI3Kα inhibitors may be effective in cance through the α-isoform,[1,2] such as:
  - Tumors with *PIK3CA* mutations
  - HER2-overexpressing tumors
- Compared to pan-PI3K inhibitors, alpelisil
  - Have an improved safety profile[3]

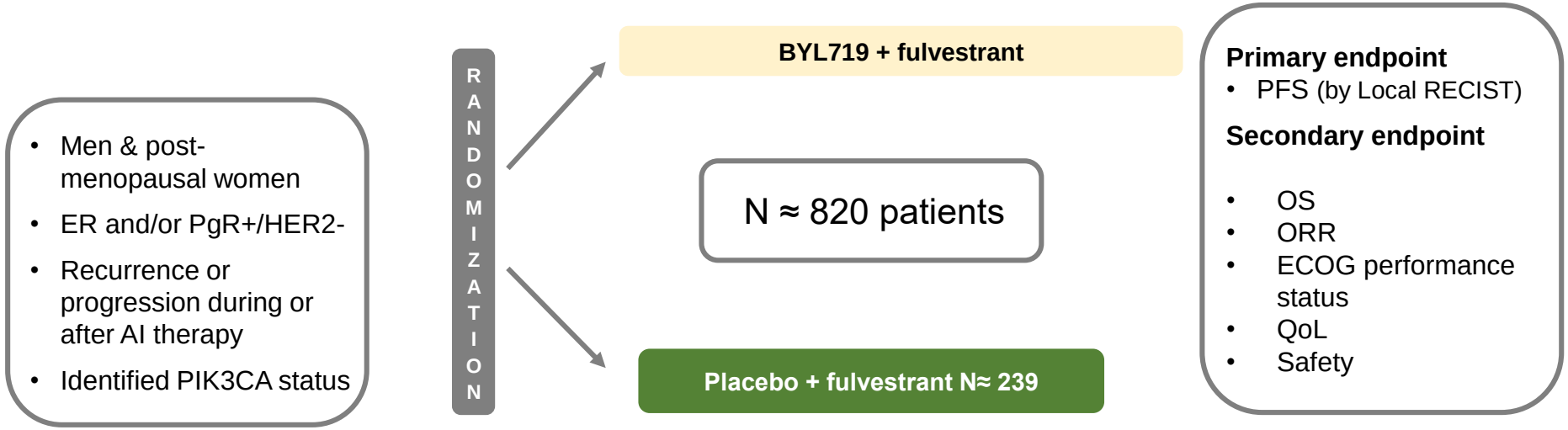


CNS, central nervous system; HER2, human epidermal growth factor receptor 2; mTORC, mammalian target of rapamycin complex;
PI3K, phosphatidylinositol 3-kinase; PIP_2, phosphatidylinositol 4,5-bisphosphate; PIP_3, phosphatidylinositol (3,4,5)-trisphosphate;
PTEN, phosphatase and tensin homolog; RTK, receptor tyrosine kinase.

1. Huang A, *et al. Cancer Research* 2012;72:abstr 3749; 2. Brana I and Siu LL. *BMC Med* 2012;10:161;
3. Jia S, *et al. Curr Opin Cell Biol* 2009;21:199–208; 4. Osborne CK, et al. *Annu Rev Med.* 2011;62:233-247
.5.Figure from https://www.novartisoncology.com

SOLAR-1: Phase III trial of Alpelisib + Fulvestrant

Phase III Randomized Double-blind, Placebo Controlled Study of Alpelisib in Combination With Fulvestrant for Men and Postmenopausal Women With Hormone Receptor Positive, HER2-negative Advanced Breast Cancer Which Progressed on or After Aromatase Inhibitor Treatment



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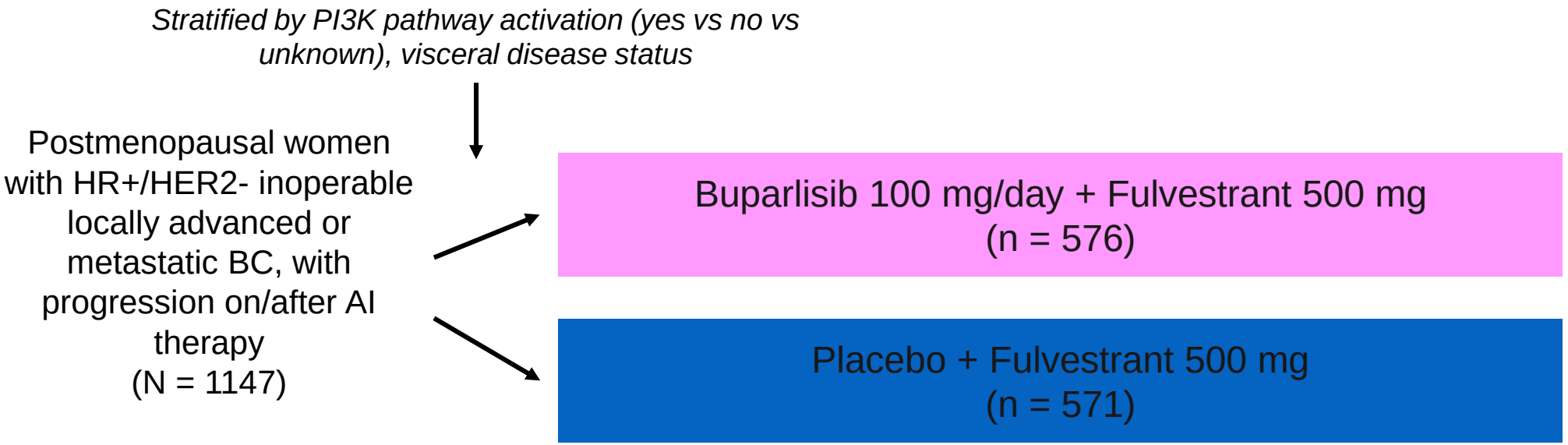
BELLE-2: Study Design



- **Primary endpoints: PFS in overall population, pts with known PI3K activation status (activated or not), and PI3K-activated only group**
- **Secondary endpoints: OS, ORR, CBR, safety, PK, QoL**
- **Exploratory endpoint: PFS by *PIK3CA* mutation status**

Baselga J, et al. SABCS 2015. Abstract S6-01.