CONTROVERSIAS EN ONCOLOGÍA
ALMERÍA

Almería, 28 de noviembre de 2019

SAOM
Sociedad Andaluza de Oncología Medica

INHIBIDORES DE CLINICAS ACTUALIZACION

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INTRODUCCION

- CMM con RH+ es una enfermedad clínica y biológicamente heterogénea.

- En estas pacientes la TE es el tratamiento de elección y se establece en base a:
- 1)IHQ ++ del RH(factores biológicos)
- 2)ILE (factores de agresividad)
- 3)La respuesta a los TH previos
- 4)La necesidad de una rápida respuesta

-CMM ***objetivo fundamental:***

-Mejorar calidad de vida

-Prolongar la supervivencia

RH+/her2: *TE pilar esencial* de tratamiento

QT:

1) Crisis amenazantes para la vida, criterios SEOM

-Insuficiencia hepática

-Linfangitis carcinomatosa, disnea incapacitante

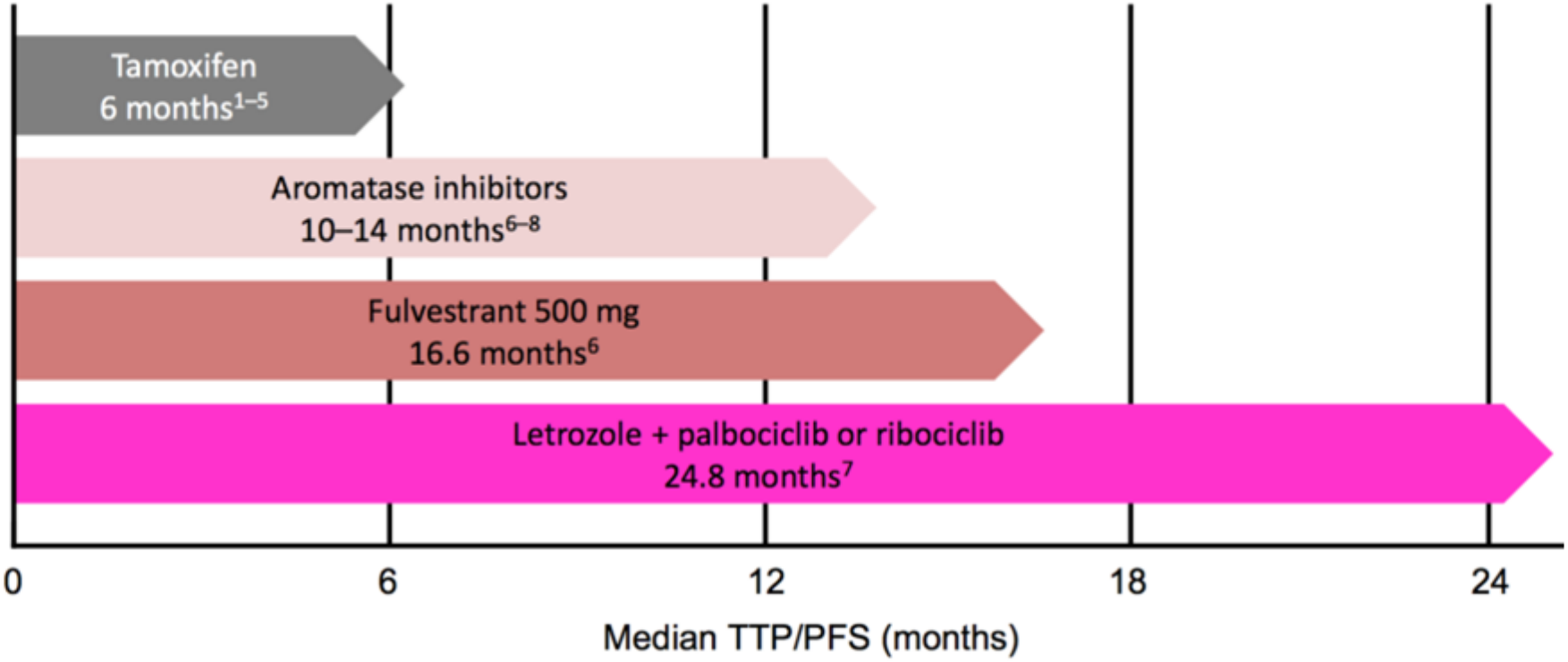
-Carcinomatosis meníngea, MTS SNC

-Infiltración MO: sintomática

-Derrame pericárdico severo

2) Refractariedad a TE previa

mbio en la Historia Natural del Cáncer de Mama Lumi



1-03. Bonneterre J, Cancer 2001. Nabholtz JM, JCO 2000. Paridaens MJ, JCO 2008. Ellis M, ESMO 2016 Finn RS, NEJM 2016. Hortobagyi G, NEJM 2016

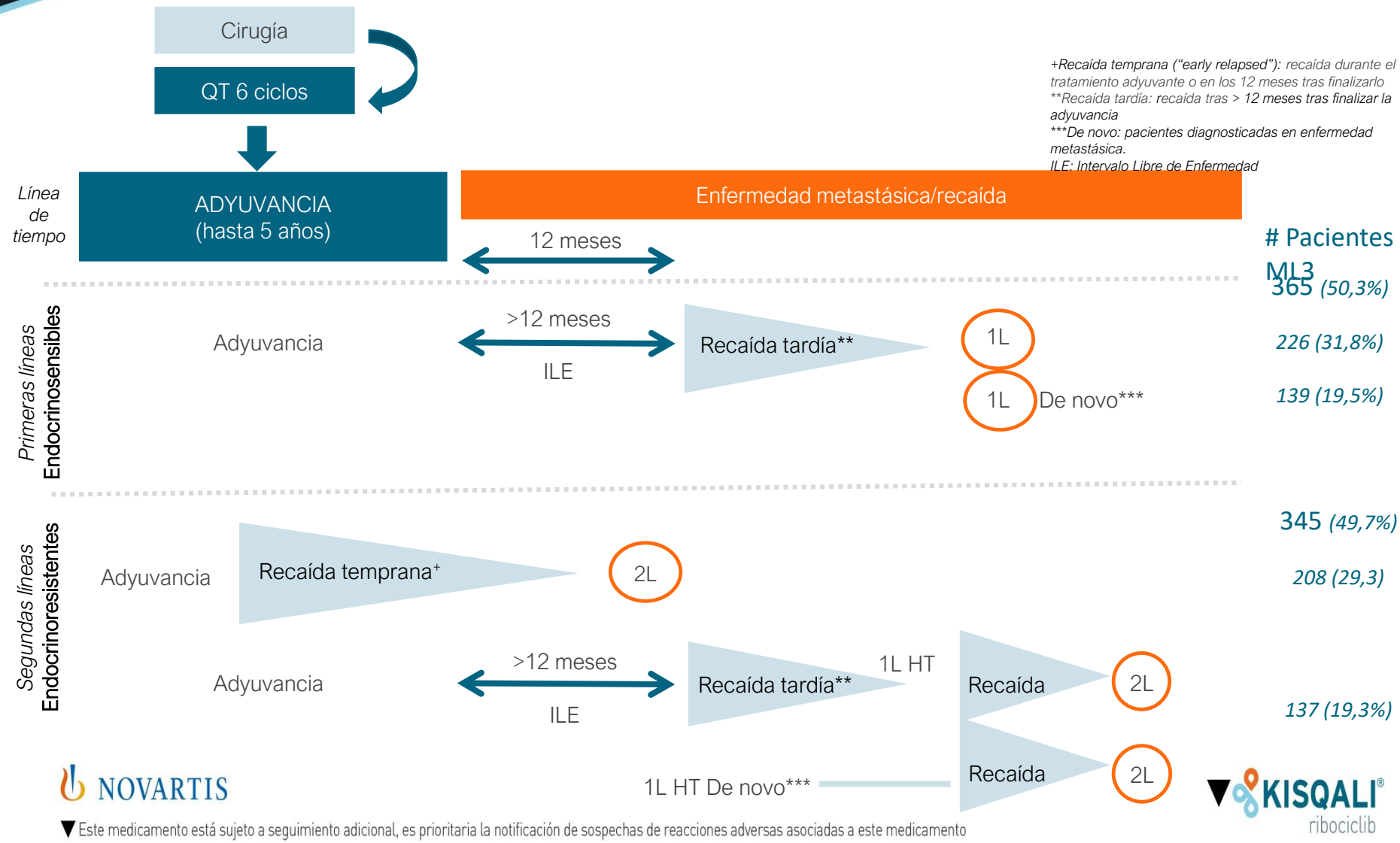
Resistencia endocrina 1ª/refractaria

- La recaída ***ocurre < dos años*** del inicio del tratamiento hormonal adyuvante
- Durante los ***6 primeros meses de la primera línea*** de tratamiento hormonal para el CMM, existe una **resistencia intrínseca primaria** o insensibilidad al tratamiento hormonal.

Resistencia secundaria

- Se produce después de haber transcurrido ***más de dos años*** del inicio del tratamiento hormonal adyuvante pero antes de un año del fin de la adyuvancia
- Progresión se produce ***después de los 6 meses*** del inicio del tratamiento hormonal para la enfermedad metastásica, existe **resistencia adquirida o secundaria**

Tipos de pacientes



+Recaída temprana ("early relapsed"): recaída durante el tratamiento adyuvante o en los 12 meses tras finalizarlo
***Recaída tardía: recaída tras > 12 meses tras finalizar la adyuvancia*
****De novo: pacientes diagnosticadas en enfermedad metastásica.*
ILE: Intervalo Libre de Enfermedad

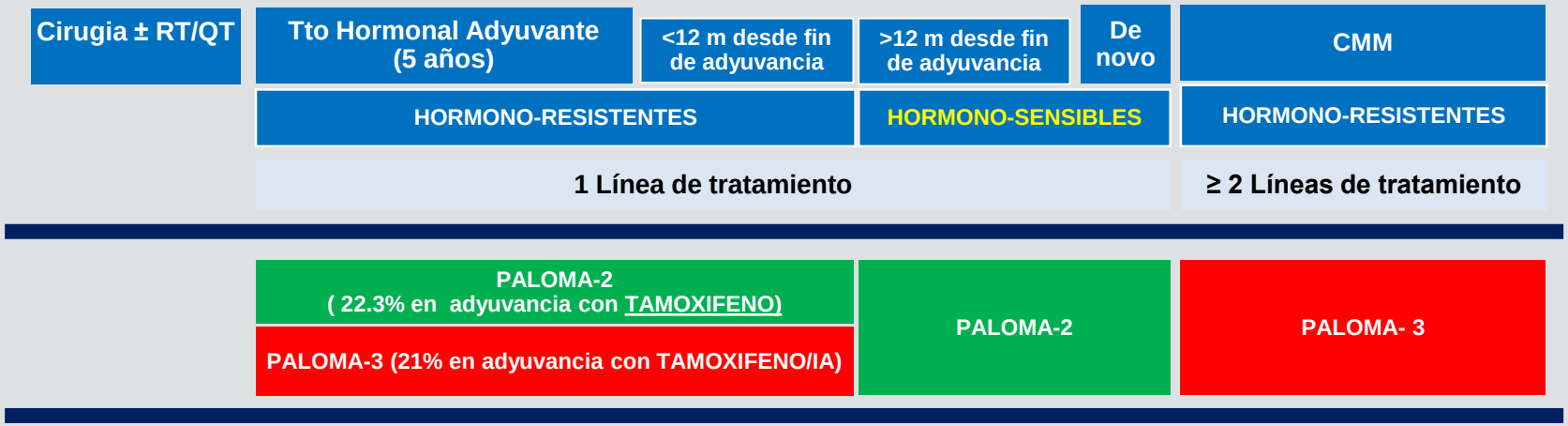
NOVARTIS

▼KISQALI® ribociclib

▼ Este medicamento está sujeto a seguimiento adicional, es prioritaria la notificación de sospechas de reacciones adversas asociadas a este medicamento

1. Slamon DJ et al. ASCO 2018;abst 1000 (oral); 2. Slamon DJ et al. J Clin Oncol 2018

Todas las poblaciones con CMm HR+/HER2- representada en sus estudios pivotales



4.1 Indicaciones terapéuticas

IBRANCE está indicado para el tratamiento del cáncer de mama metastásico o localmente avanzado, positivo para el receptor hormonal (HR) y negativo para el receptor 2 del factor de crecimiento epidérmico humano (HER2):

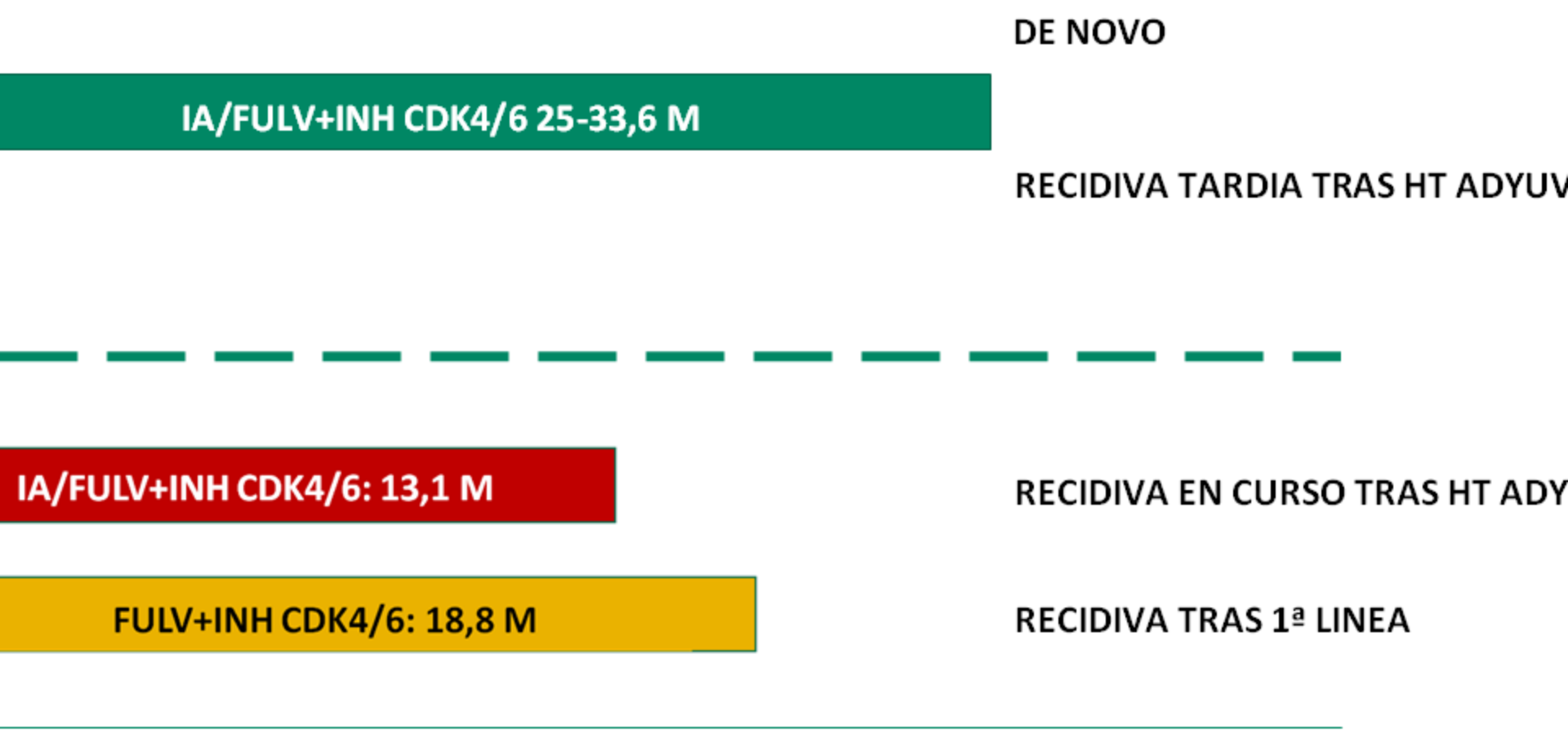
- en combinación con un inhibidor de la aromatasa;
- en combinación con fulvestrant en mujeres que hayan recibido hormonoterapia previa (ver sección 5.1).

En mujeres pre o perimenopáusicas la hormonoterapia se debe combinar con un agonista de la hormona liberadora de la hormona luteinizante (LHRH).

IBRANCE® palbociclib

Creado a partir de 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. Turner NC et al. , Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer 2015 N Engl J Med. 3. Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol. 2016;17(4):425-39. // 4. FT de Ibrance.

¿Qué nos aportan los inhibidores de ciclinas en CMM?



Finn RS, NEJM 2016. Hortobagyi G, NEJM 2016. Goetz MP, JCO 2017. Turner NC, NEJM 2015. Sledge GW, JCO 2017..

Contents lists available at ScienceDirect

The Breast

jou rnal homepage : www.elsevier.com / brst

Original article

3rd ESO-ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3)

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-20)

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)
- Palbociclib + aromatase inhibitor (category 1)[2,3]
- Palbociclib + fulvestrant (category 1)[2,4]
- Ribociclib + aromatase inhibitor (category 1)[2,3]
- Abemaciclib + aromatase inhibitor (category 1)[2,3]
- Abemaciclib + fulvestrant (category 1)[2,3]
- Exemestane + everolimus[2,6]
- Fulvestrant + everolimus
- Tamoxifen + everolimus
- Ribociclib + tamoxifen (category 1)[2,7]

Useful in certain circumstances:
- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol
- Abemaciclib[2,8]

HER2-Positive and Premenopausal
See Systemic Treatment of Stage IV (M1) Disease (BINV-22)

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

[1]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.

[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]CDK4/6 inhibitor 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.

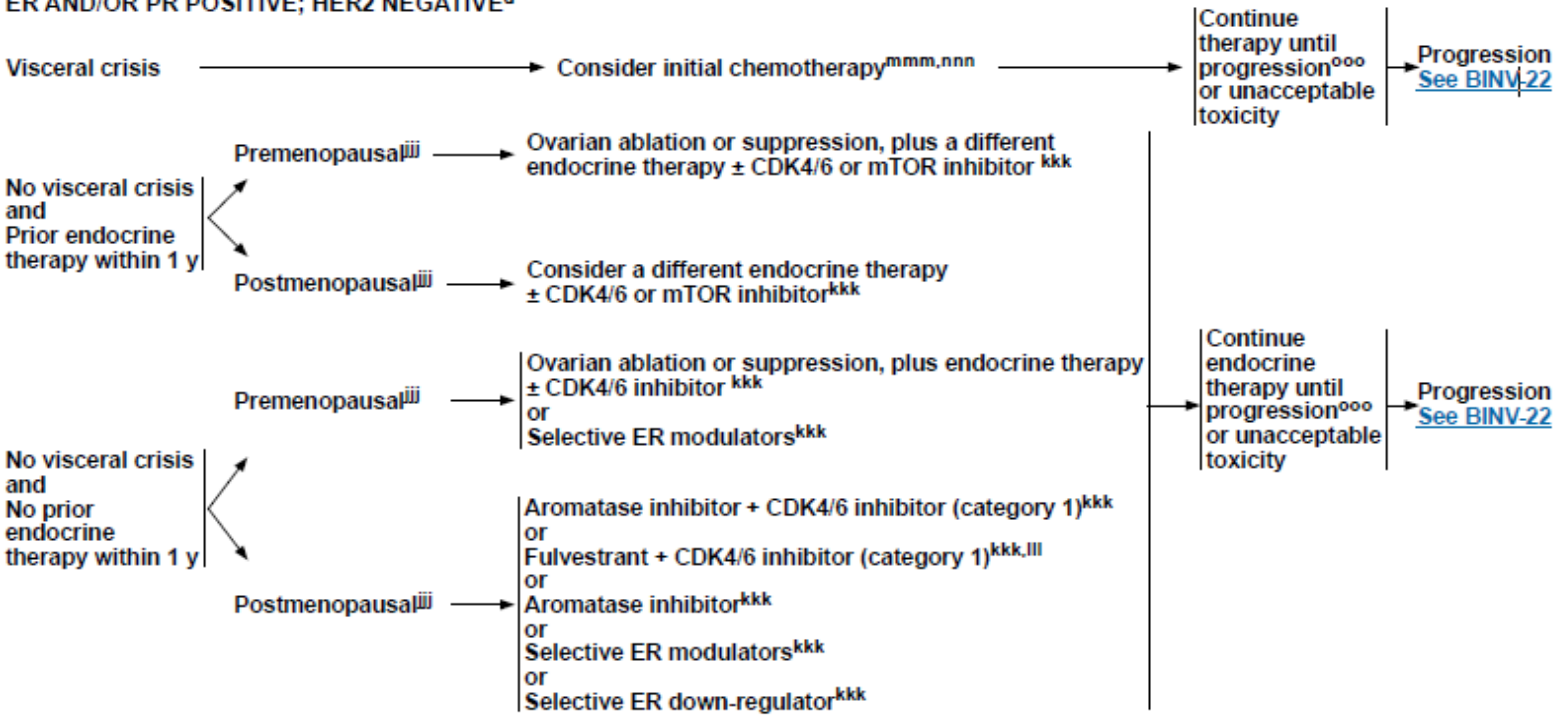
[6]A combination of exemestane with everolimus can be considered for patients who meet the eligibility criteria for BOLERO-2 (progressed within 12 mo or on non-steroidal AI).

[7]May be considered 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.

[8]Indicated 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.

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV (M1) DISEASE: ER AND/OR PR POSITIVE; HER2 NEGATIVE[d]



[d] See Principles of HER2 Testing (BINV-A).
[lll] See Definition of Menopause (BINV-Q).
[kkk] See Systemic Therapy for ER- and/or PR-Positive Recurrent or Stage IV (M1) Disease (BINV-P).
[lll] Fulvestrant has been combined with CDK4/6 inhibitors (palbociclib, ribociclib) in the first-line setting in two randomized trials.

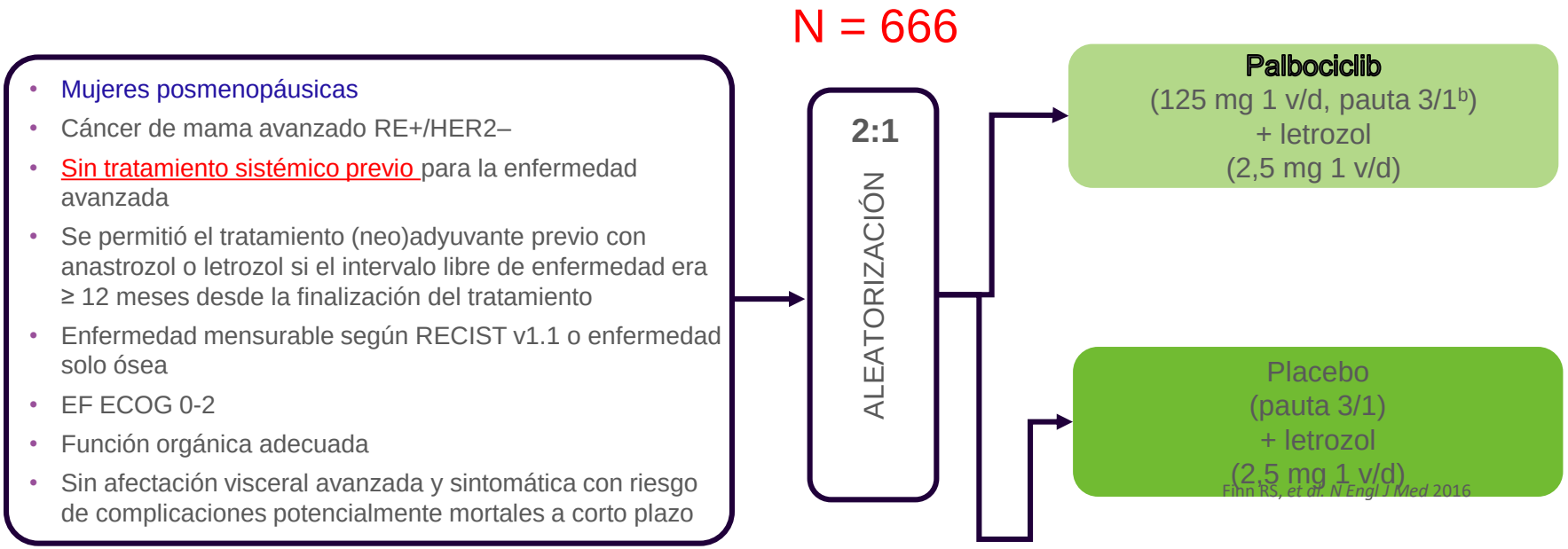
[mmm] See Chemotherapy Regimens for Recurrent or Stage IV (M1) Disease (BINV-Q).
[nnn] Consider PARP-inhibitor monotherapy as an option for patients with HER2-negative tumors and germline *BRCA1/2* mutations.
[ooo] See Principles of Monitoring Metastatic Disease (BINV-R).

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.

1ª línea

(HORMONOSENSIBLES)

PALOMA-2: Diseño del estudio de fase III en pacientes posmenopáusicas con CMM RE+/ HER2–



[a]Aleatorización estratificada por la localización de la enfermedad (visceral/no visceral), el intervalo libre de enfermedad y el tratamiento hormonal (neo)adyuvante previo

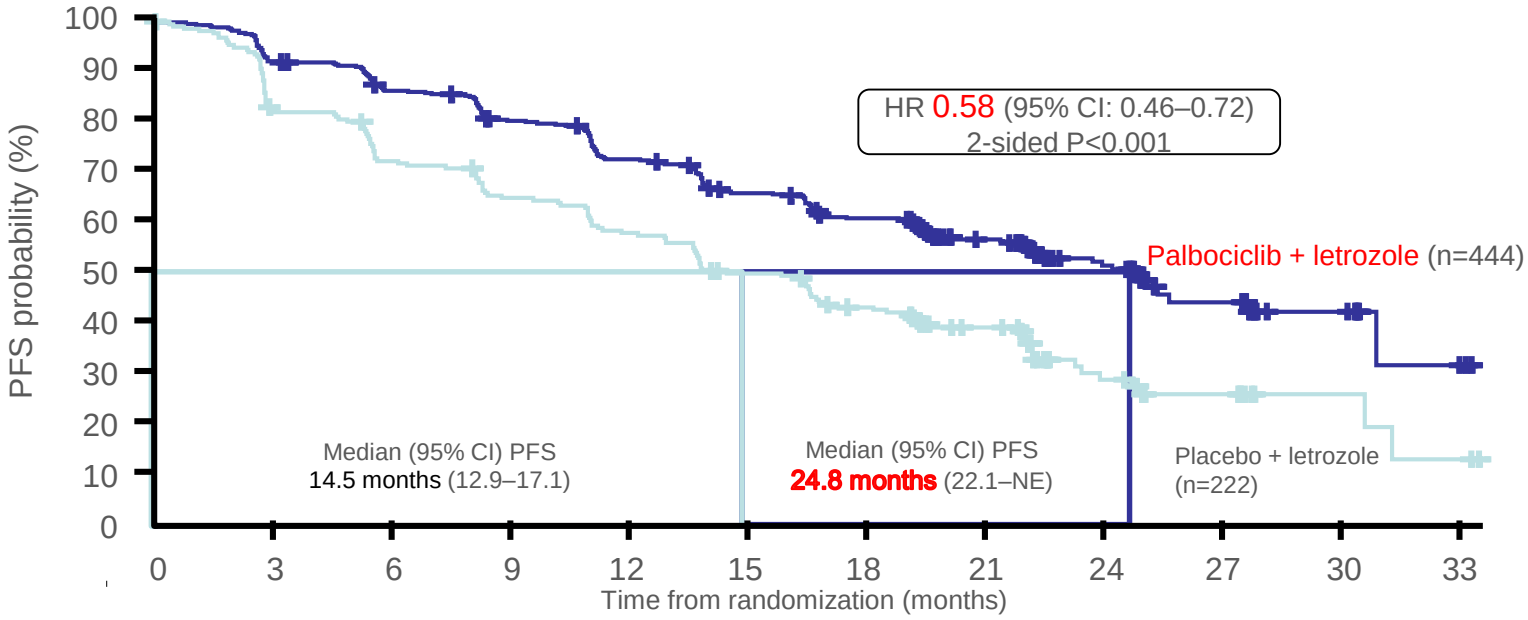
[b]3 semanas con tratamiento/1 semana sin tratamiento de un ciclo de 4 semanas

Anastrozol, laboratorio comercializador Astrazeneca; 1 v/d, una vez al día; EF ECOG, estado funcional del *Eastern Cooperative Oncology Group*; HER2, receptor 2 del factor de crecimiento epidérmico humano; RE, receptor de estrógenos; RECIST, Criterios de Evaluación de la Respuesta en Tumores Sólidos

clinicaltrials.gov NCT01740427; Finn RS, *et al.* N Engl J Med 2016

PALOMA-2: SLP evaluada por el investigador (población ITT)

- Como tratamiento inicial para mujeres posmenopáusicas con cáncer de mama avanzado RE+/HER2–, palbociclib + letrozol mejoró significativamente la SLP frente a placebo + letrozol



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

Extraído de Finn RS, *et al.* N Engl J Med 2016

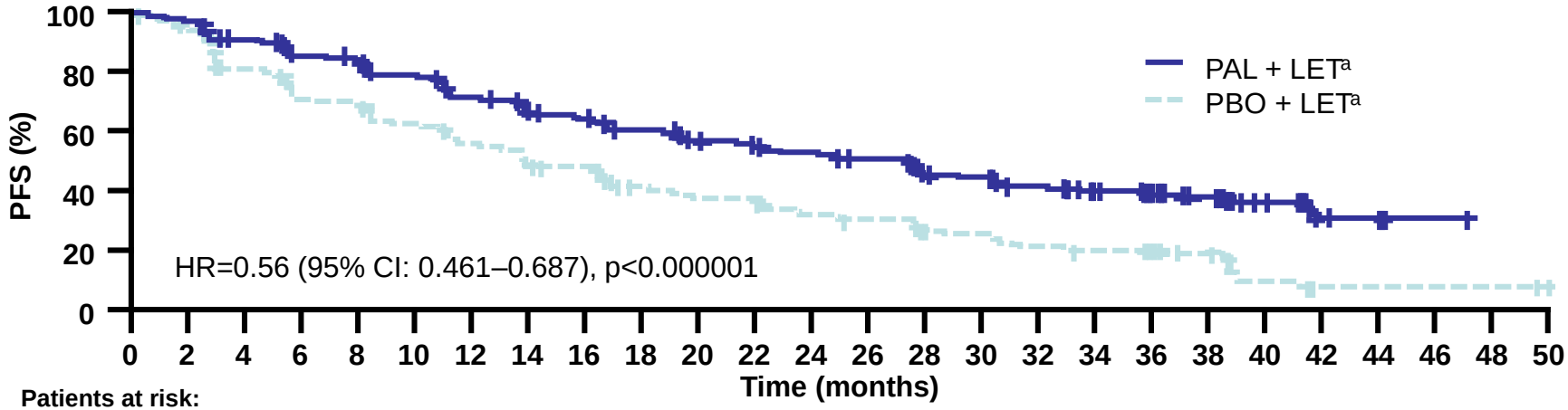
CI, intervalo de confianza; HER2, receptor 2 del factor de crecimiento epidérmico humano; HR, hazard ratio; ITT, intención de tratar; LET, letrozol; NE, no estimable; PAL, palbociclib; PCB, placebo; RE, receptor de estrógenos; SLP, supervivencia libre de progresión

PALOMA 2-Assessed PFS

mPFS Update after > 37 month follow-up

Investigator-assessed PFS[a]

	Data cutoff date: February 26, 2016[b]		Data cutoff date: May 31, 2017[c]	
	PAL + LET	PBO + LET	PAL + LET	PBO + LET
mPFS, months (95% CI)	24.8 (22.1–NE)	14.5 (12.9–17.1)	27.6 (22.4–30.3)	14.5 (12.3–17.1)
PFS HR (95% CI)	0.576 (0.463–0.718)		0.563 (0.461–0.687)	
1-sided p value	<0.000001		<0.000001	



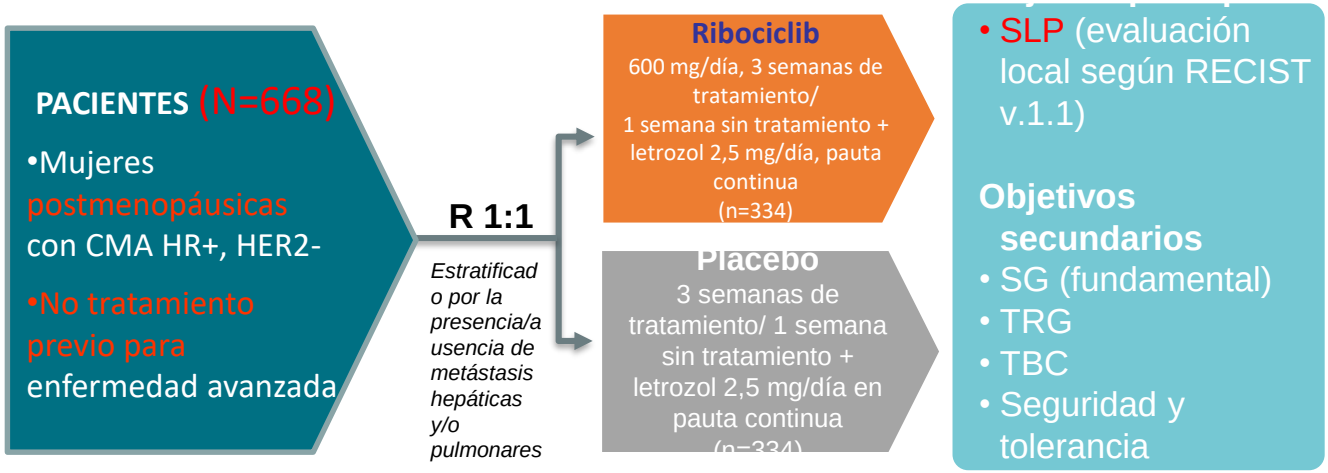
Patients at risk:

PAL + LET	444	424	391	359	353	325	294	268	260	239	224	216	204	192	168	164	150	126	83	64	24	5	4	2	0
PBO + LET	222	204	169	147	143	128	114	100	96	80	73	70	61	55	46	45	38	34	26	19	5	2	2	2	2	0

[a]Data cutoff, May 31, 2017 [b]Median follow-up duration was 23.0 months in the palbociclib + letrozole arm and 22.3 months in the placebo + letrozole arm; [c]Median follow-up duration was 37.6 months in the palbociclib + letrozole arm and 37.3 months in the placebo + letrozole arm CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; LET, letrozole; mPFS, median PFS; NE, not estimable; PAL, palbociclib; PBO, placebo; PFS, progression-free survival

Rugo HS, et al. Breast Cancer Res Treat. 2019 Jan 10.

MONALEESA-2:
Fase III ribociclib + letrozol en CMA HR+, HER2-[1,2]



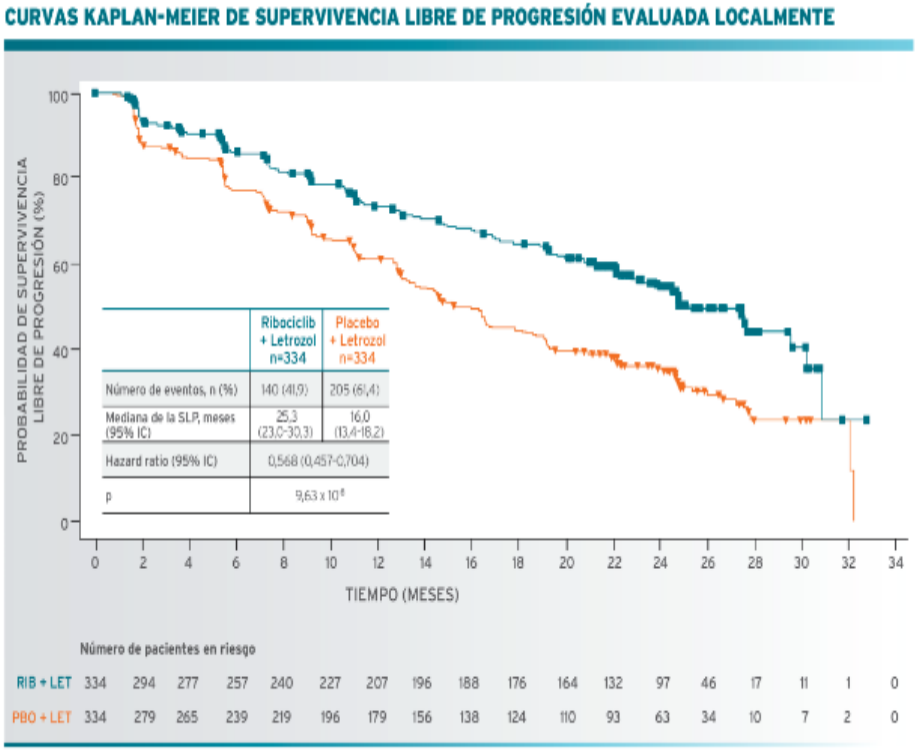
- Las evaluaciones tumorales se realizaron cada 8 semanas durante los primeros 18 meses, y después cada 12 semanas
- El análisis final estaba planificado después de 302 eventos de SLP–93,5% de potencia para detectar una reducción del riesgo de 33% (hazard ratio 0.67) con α=2,5% unilateral
- El análisis intermedio se planificado después de ~70% eventos de SLP–Criterios de parada: *Two-look Haybittle–Peto*: hazard ratio ≤0,56 y p <0,0000129
- En la fecha de corte de los datos para el análsis intermedio (29 enero 2016), se habían producido 243 eventos de SLP (80% fracción de información)

CMA: cáncer de mama avanzado; TBC: tasa de beneifico clínico; HER2–: receptor del factor de crecimiento epidérmico humano 2-negativo; HR+: recpeptor hormonal positivo; TRG: tasa de respuesta global; SG: supervivencia global; SLP: supervivencia libre de progresión; QoL: calidad de vida; R: randomización; RECIST: Criterios de Evaluación de Respuesta en Tumores Sólidos.

1. Hortobagyi GN et al. N Engl J Med 2016;375:1738-48. **2.** Hortobagyi GN et al. Ann Oncol 2016;27(Suppl 6): abstr LBA 3552 (oral).

Evidencia clínica en combinación:
fase III Monaleesa 2 (SLP)

En un análisis posterior con 11 meses adicionales de seguimiento, la mediana de la SLP fue de 25,3 meses con KISQALI + letrozol frente a 16,0 meses con placebo + letrozol (HR=0,568 [IC del 95%:



IC: intervalo de confianza; LET: letrozol; PBO: placebo; RIB: ribociclib.
Corte de datos 2 de enero de 2017

Updated results from MONALEESA-2, a phase 3 trial of first-line ribociclib + letrozole in hormone receptor-positive (HR+), HER2-negative (HER2–), advanced breast cancer (ABC).

1. Hortobagyi GN et al. American Society de Clinical Oncology Annual Meeting; 2017; Poster 1038.

MONARCH 3: Study Design

Inclusion Criteria

- ER+, HER2- MBC
- Postmenopausal
- Metastatic or locoregionally recurrent disease with no prior systemic therapy in this setting
- If (neo)adjuvant ET administered, a disease free interval of >12 months since completion of ET
- ECOG PS ≤1

N=493

2:1 Randomization

Abemaciclib

150 mg BID (continuous schedule) plus

Anastrozole

1 mg or[a] **letrozole:** 2.5 mg QD until PD

Placebo: BID (continuous schedule) plus

Anastrozole: 1 mg or[a]

letrozole: 2.5 mg QD until PD

Primary endpoint:
Investigator-assessed PFS
Secondary endpoint:
OS, Response rates, Safety
Stratification factors:

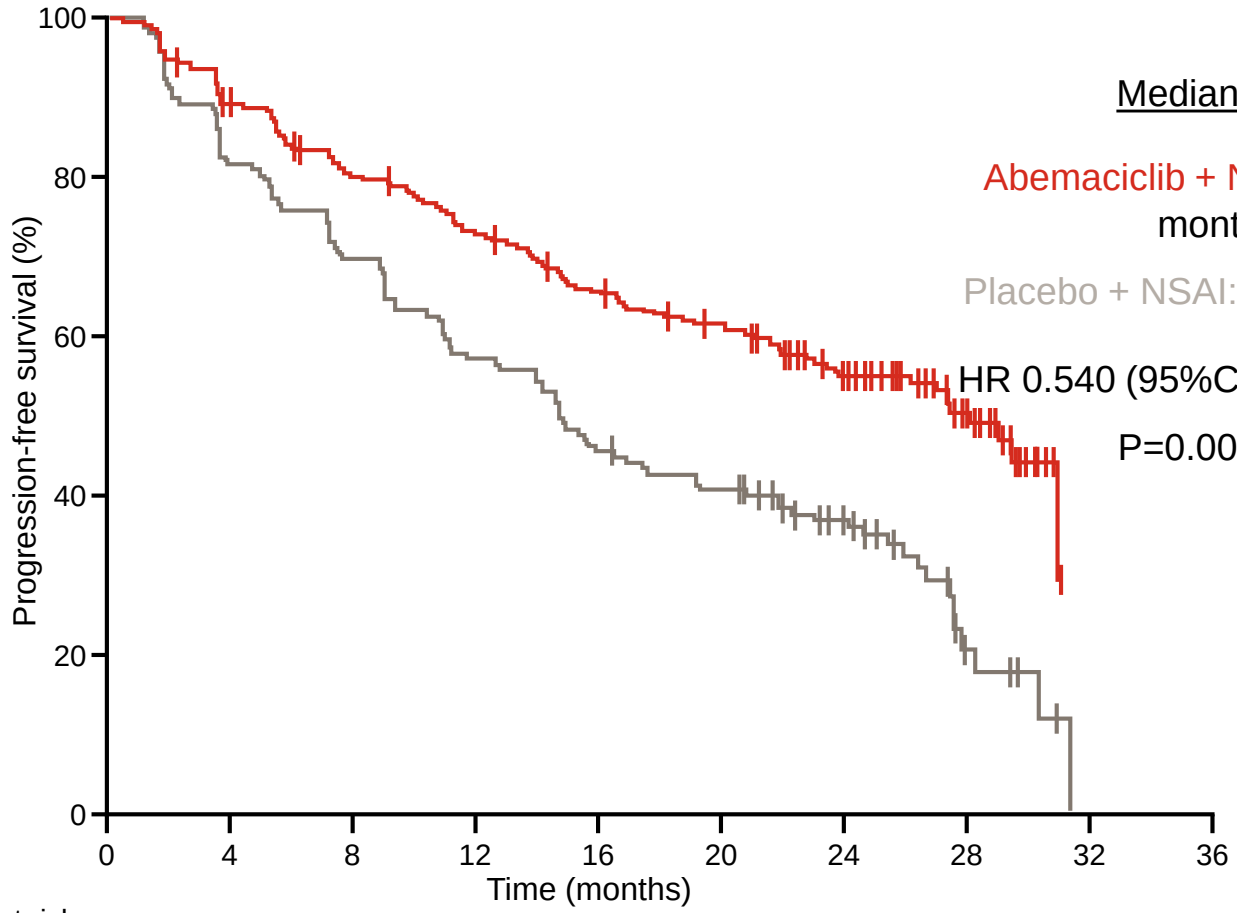
- Metastatic site (visceral, bone only, or other)
- Prior ET (AI, no ET, or other)

[a]per physician's choice: 79.1% received letrozole, 19.9% received anastrozole

- ✓ Statistics: 240 PFS events for 80% power at one-sided α of 0.025 assuming a hazard ratio of 0.67
- ✓ Enrolment: From November 2014 to November 2015 patients enrolled in 158 centres from 22 countries
- ✓ Median follow-up: 26.7 months (final analysis)
- ✓ Overall Survival (OS): Immature at this time

Goetz MP, *et al. J Clin Oncol* 2017;35:3638–46.

MONARCH 3: Investigator-Assessed PFS



Median PFS

Abemaciclib + NSAI: 28.18 months

Placebo + NSAI: 14.76 months

HR 0.540 (95%CI 0.418, 0.698)

P=0.000002

Patients at risk:

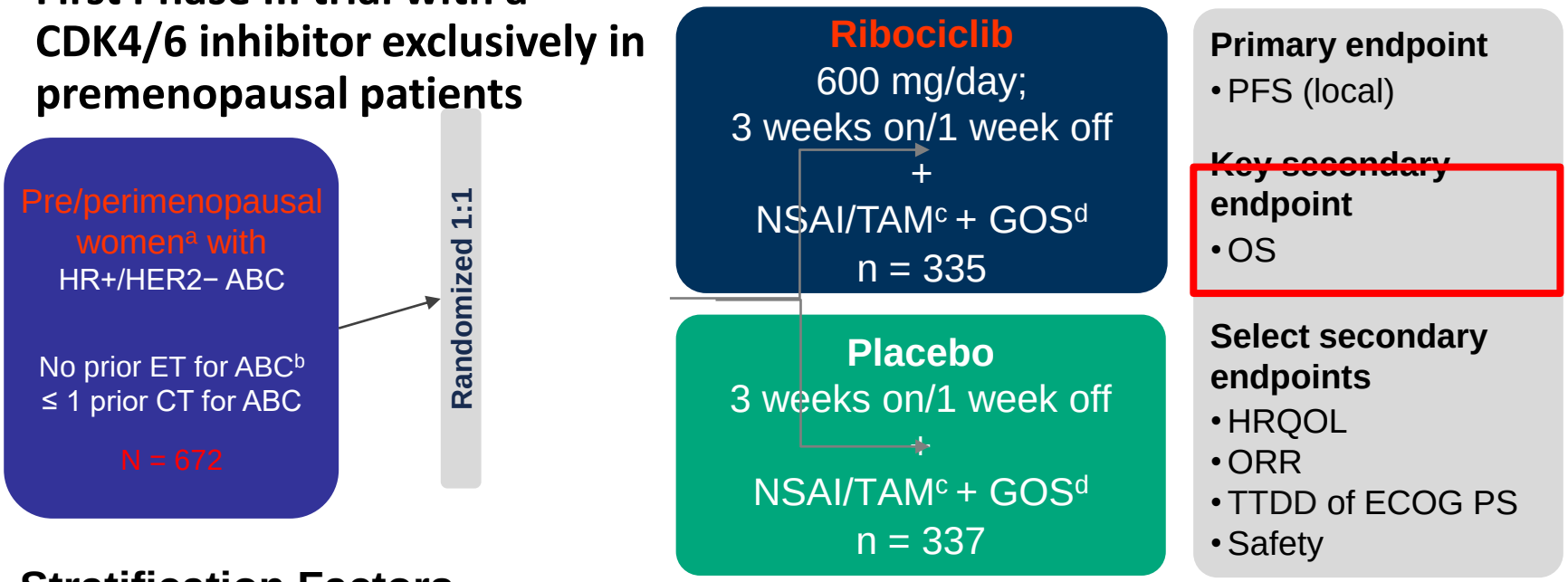
abemaciclib	328	272	236	208	181	164	106	40	0	0
placebo	165	126	105	84	66	58	42	7	0	0

Gráfica adaptada de: Goetz MP, *et al.* *J Clin Oncol* 2017;35:3638–4

Goetz MP, *et al. J Clin Oncol* 2017;35:3638–46.

MONALEESA-7 Study Design

First Phase III trial with a CDK4/6 inhibitor exclusively in premenopausal patients



Stratification Factors

- Liver/lung metastasis (yes/no)
- Prior chemotherapy (yes/no)
- Combination partner (NSAI/TAM)

P3: 1906067

, anastrozole; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; FSH, follicle-stimulating hormone; GOS, goserelin; HRQOL, health-related quality of life; NSAI, nonsteroidal aromatase inhibitor; ORR, objective response rate; TAM, tamoxifen; TTDD, time to definitive deterioration.

[a] Premenopausal status was defined as either patient had last menstrual period ≤ 12 months ***or*** if receiving TAM or toremifene for ≤ 14 days, plasma estradiol and FSH must be in normal premenopausal range ***or*** in the case of induced amenorrhea, plasma estradiol and FSH must be in normal premenopausal range. Perimenopausal status was defined as neither premenopausal nor postmenopausal (prior bilateral oophorectomy, age ≥ 60 years, or FSH and plasma estradiol levels in normal postmenopausal range). Patients could not be ≥ 60 years of age. [b] Patients who received ≤ 14 days of NSAI/TAM ± GOS were allowed. [c] TAM and NSAI were administered daily orally. TAM dose was 20 mg, LET dose was 2.5 mg. and ANA dose was 1 mg. [d] GOS 3.6 mg was administered by subcutaneous injection. ANA

MONALEESA 7

Primary endpoint: PFS (investigator-assessed)

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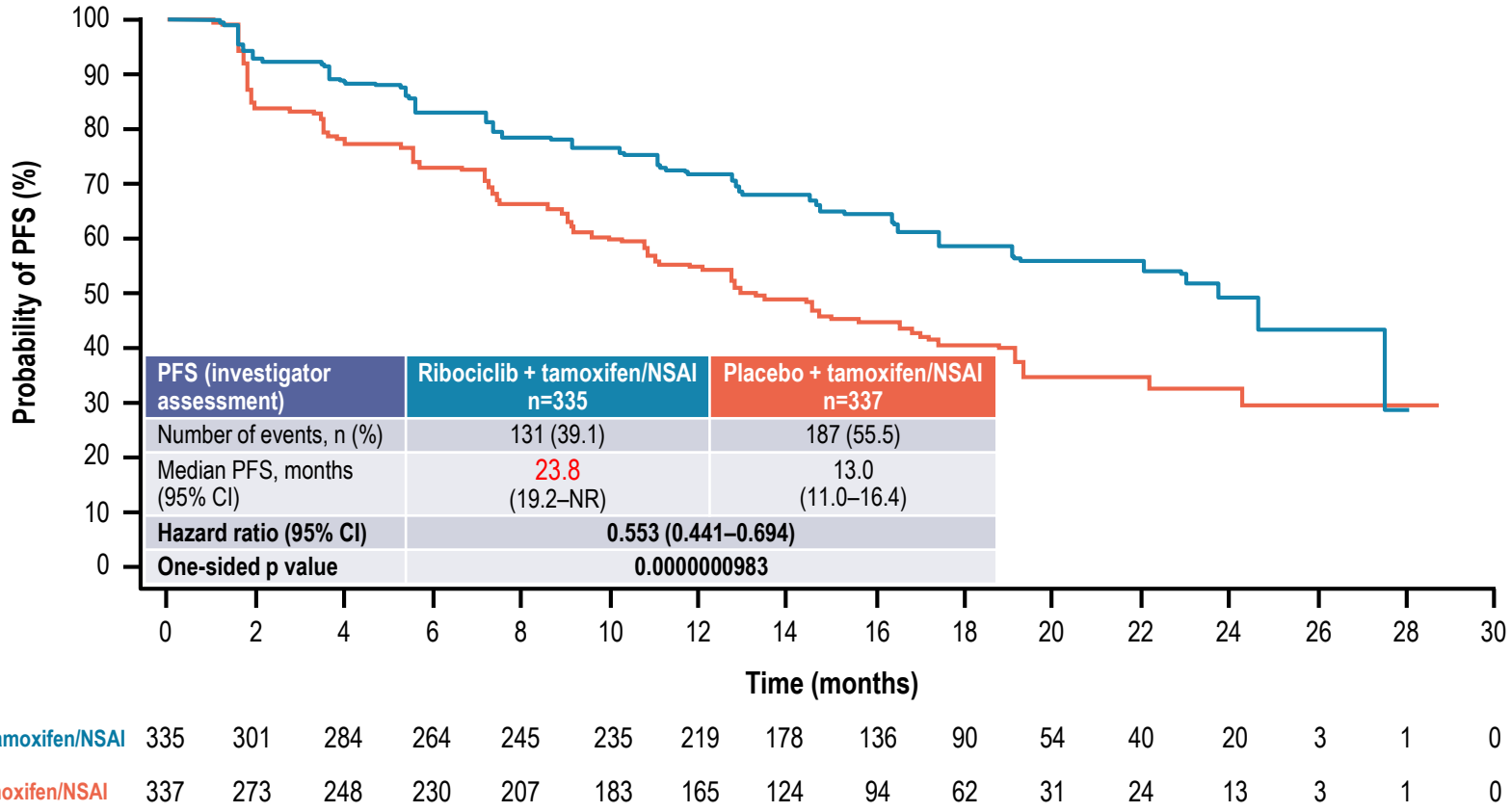


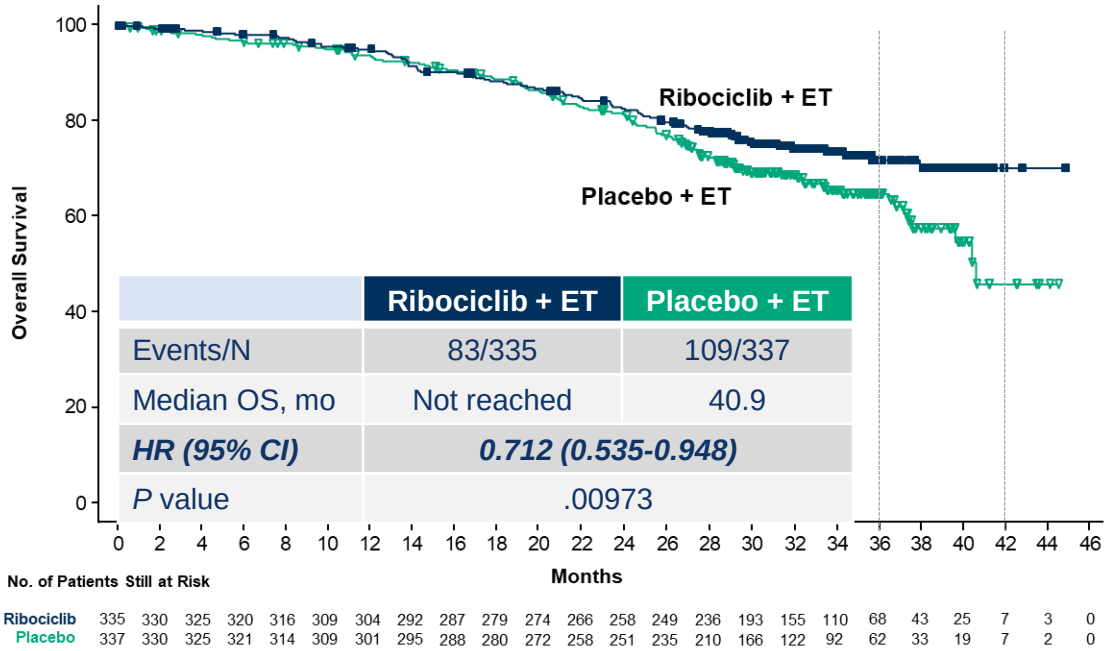
PFS (investigator assessment)	Ribociclib + tamoxifen/NSAI n=335	Placebo + tamoxifen/NSAI n=337
Number of events, n (%)	131 (39.1)	187 (55.5)
Median PFS, months (95% CI)	23.8 (19.2–NR)	13.0 (11.0–16.4)
Hazard ratio (95% CI)	**0.553 (0.441–0.694)**	
One-sided p value	**0.0000000983**	

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.

MONALEESA 7: Overall Survival



	Ribociclib + ET	Placebo + ET
Events/N	83/335	109/337
Median OS, mo	Not reached	40.9
HR (95% CI)	***0.712 (0.535-0.948)***	
P value	.00973	

- ≈ 29% relative reduction in risk of death
- The *P* value of .00973 crossed the prespecified boundary to claim superior efficacy

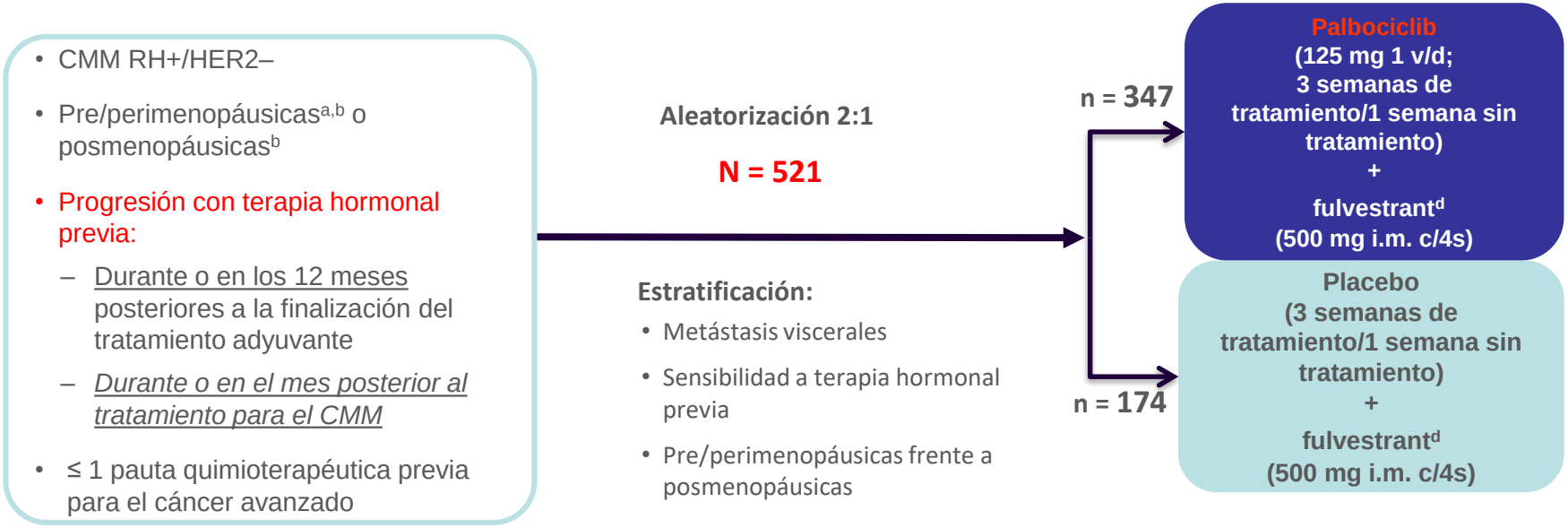
Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	71.9%	64.9%
42 months	***70.2%***	***46.0%***

2ª Línea
(Hormonorresistentes)

PALOMA-3: Diseño del estudio[1–4]

Estudio de fase III doble ciego en 144 centros de 17 países (NCT01942135)



Turner *et al.* 2015[1]

[a]Todas recibieron goserelina; [b]Deben haber progresado con tamoxifeno adyuvante u otra terapia hormonal previa (pre/perimenopáusicas) o tratamiento con IA (posmenopáusicas); [c]Pacientes aleatorizadas; [d]Administrado los días 1 y 15 del ciclo 1 y, posteriormente, cada 28 días. Fecha de corte de los datos de 5 de diciembre de 2014 utilizada para el análisis provisional; mediana de seguimiento de 5,6 meses. Fecha de corte de los datos de 16 de marzo de 2015 utilizada para el análisis final; mediana de seguimiento de 8,9 meses. Fulvestrant: Laboratorio comercializador AstraZeneca.

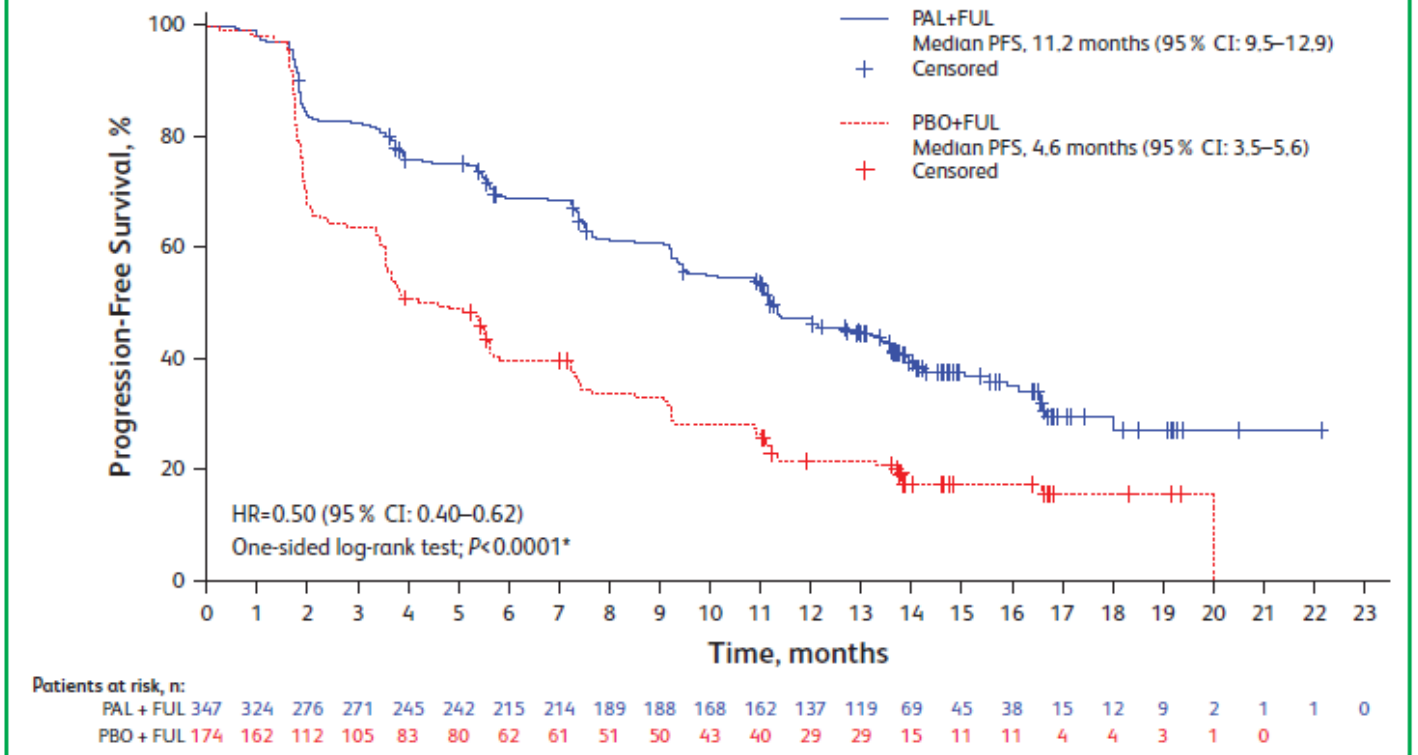
CMM, cáncer de mama metastásico; HER2, receptor 2 del factor de crecimiento epidérmico humano; IA, inhibidor de la aromatasa; i.m., intramuscular.

1. Turner NC, *et al.* N Engl J Med 2015. 2. Cristofanilli M, *et al.* Lancet Oncol 2016. 3. Harbeck N, *et al.* Annals Oncol 2016.

4. Verma S, *et al.* The Oncologist 2016

Ibrance: Más del doble de SLP en pacientes hormonorresistentes

Figure 2. Progression-Free Survival: Updated Analysis of ITT Population



CI=confidence interval; FUL=fulvestrant; HR=hazard ratio; ITT=intent-to-treat; PAL=palbociclib; PBO=placebo; PFS=progression-free survival.
*Stratified by the presence of visceral disease and sensitivity to prior hormone therapy.

HR = 0,50
(95% CI: 0,4 – 0,62)

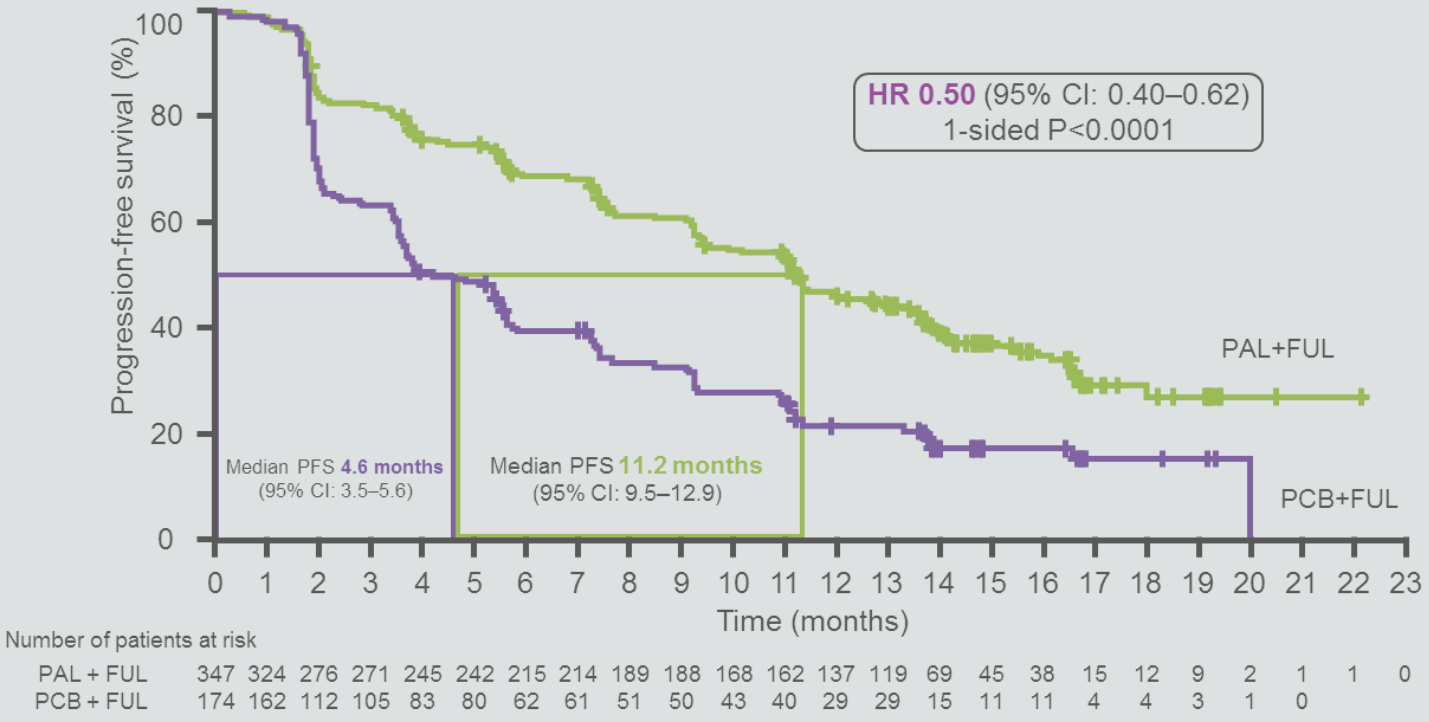
Ibrance + Fulvestrant
Mediana (95% IC)
SLP **11,2 meses**
(9,5 – 12,9)

Placebo + Fulvestrant
Mediana (95% IC)
SLP **4,6** months
(3,5 – 5, 6)

Extraído de Turner, et al. N Engl J Med 2018

IBRANCE® palbociclib

Reducción del riesgo de progresión de tumor en un 50%[1]



Extraído de Turner, et al. N Engl J Med 2018

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SLP **4,6** months
(3,5 – 5, 6)

1. Turner NC, *et al*. NEJM 2018

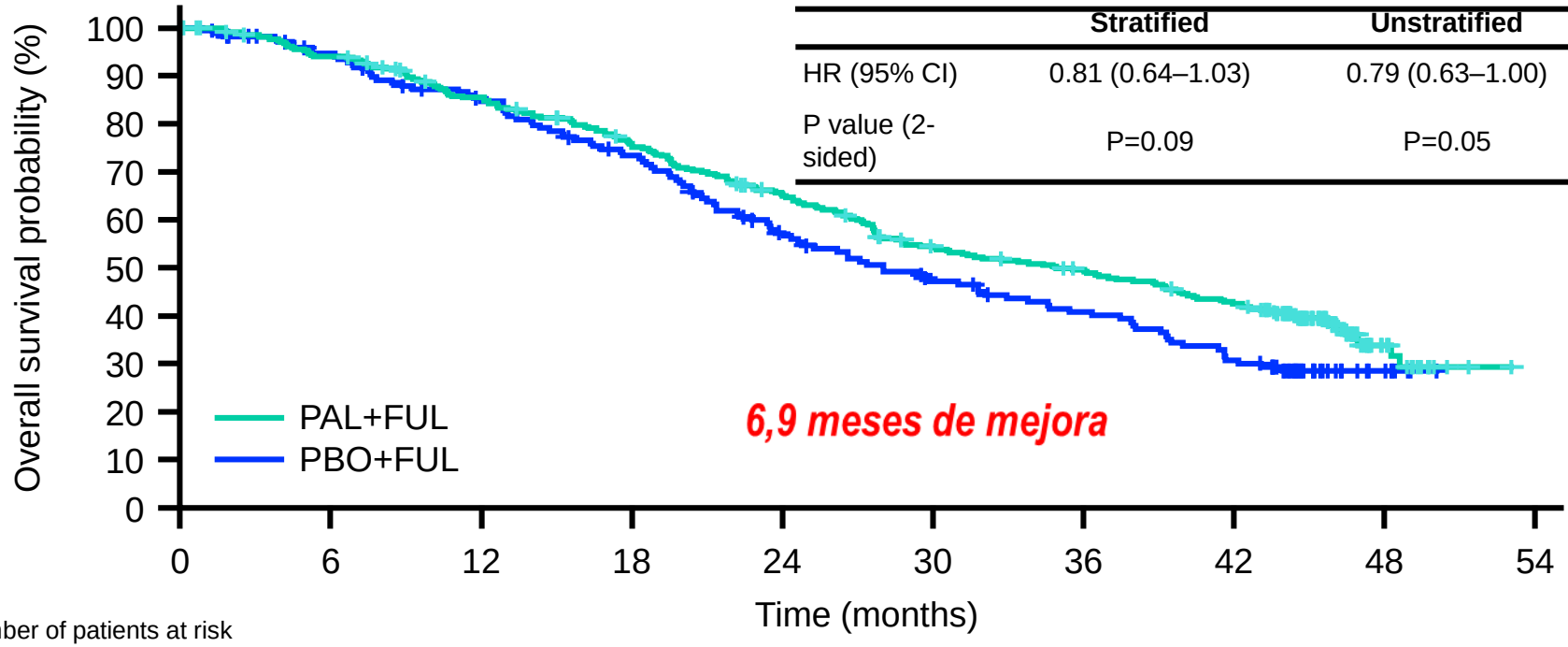
*Fecha de corte de los datos: octubre de 2015

CI, intervalo de confianza; CMM, cáncer de mama metastásico; FUL, fulvestrant; HER2, receptor 2 del factor de crecimiento epidérmico humano; HR, hazard ratio; PAL, palbociclib; PCB, placebo; RH, receptor hormonal; SLP, supervivencia libre de progresión

Overall Survival in PALOMA-3 (ITT) *ESMO 2018*

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

	PAL+FUL (n=347)	PBO+FUL (n=174)
Median OS, Month (95% CI)	34.9 (28.8–40.0)	28.0 (23.6–34.6)
	Stratified	**Unstratified**
HR (95% CI)	0.81 (0.64–1.03)	0.79 (0.63–1.00)
P value (2-sided)	P=0.09	P=0.05



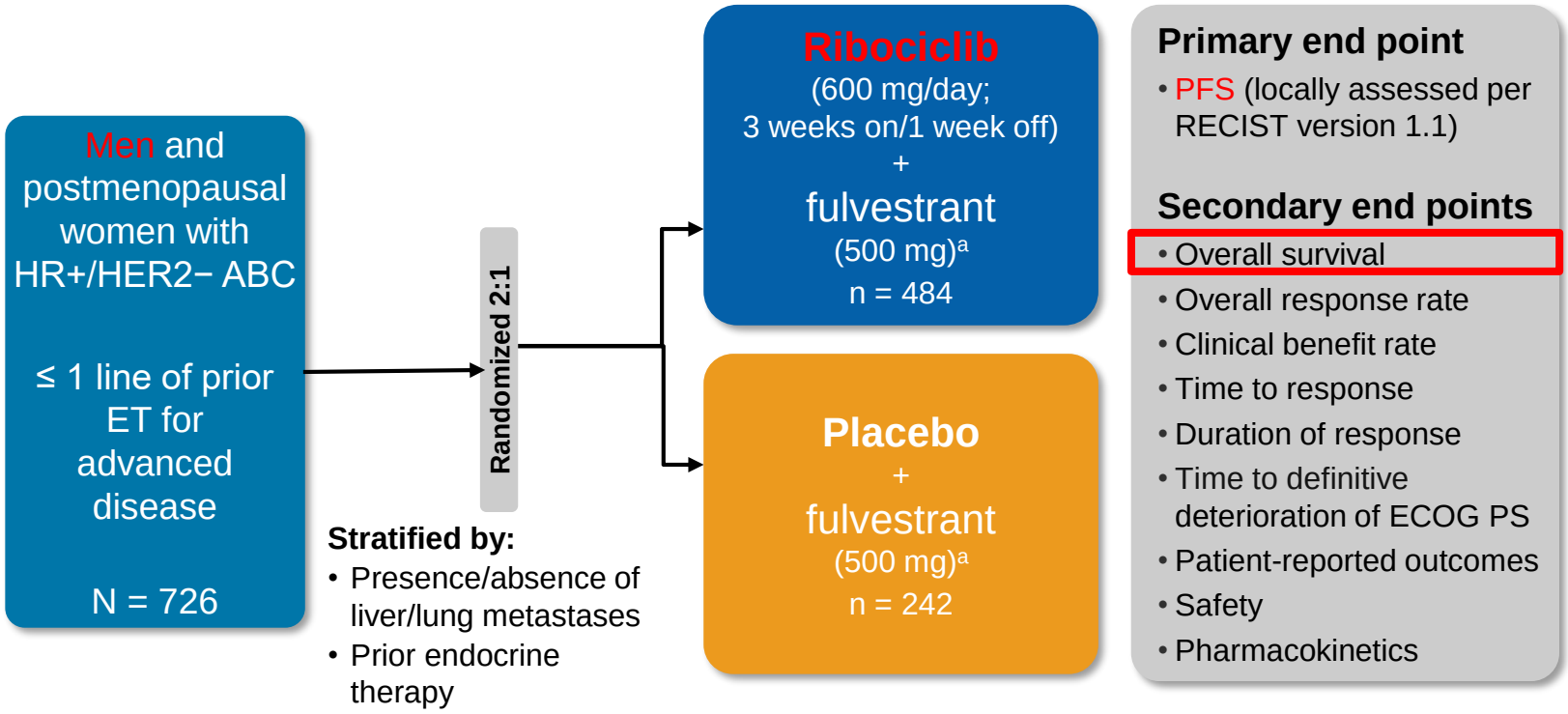
Number of patients at risk

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

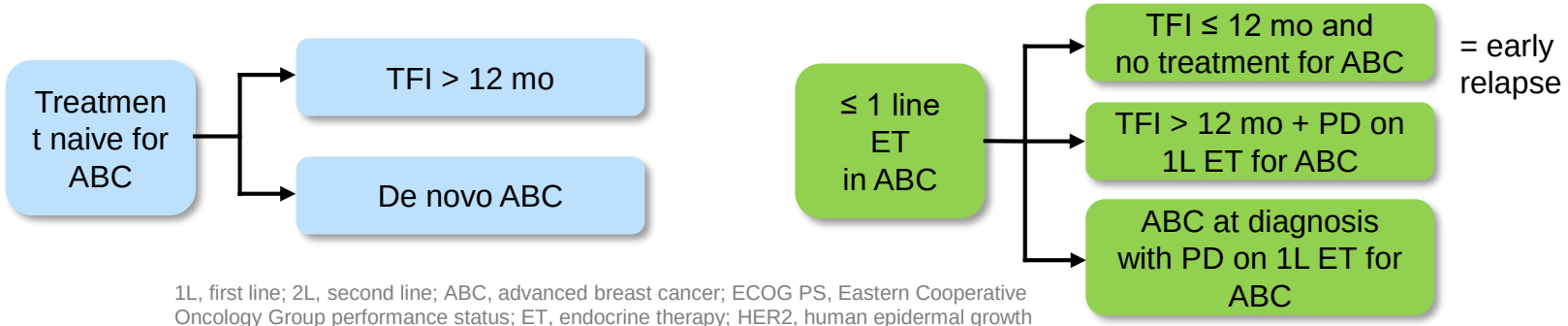
FUL=fulvestrant; HR=hazard ratio; ITT=intent-to-treat; OS=overall survival; PAL=palbociclib; PBO=placebo.

Turner, et al. N Engl J Med 2018

MONALEESA-3 Study Design



Patient population definitions

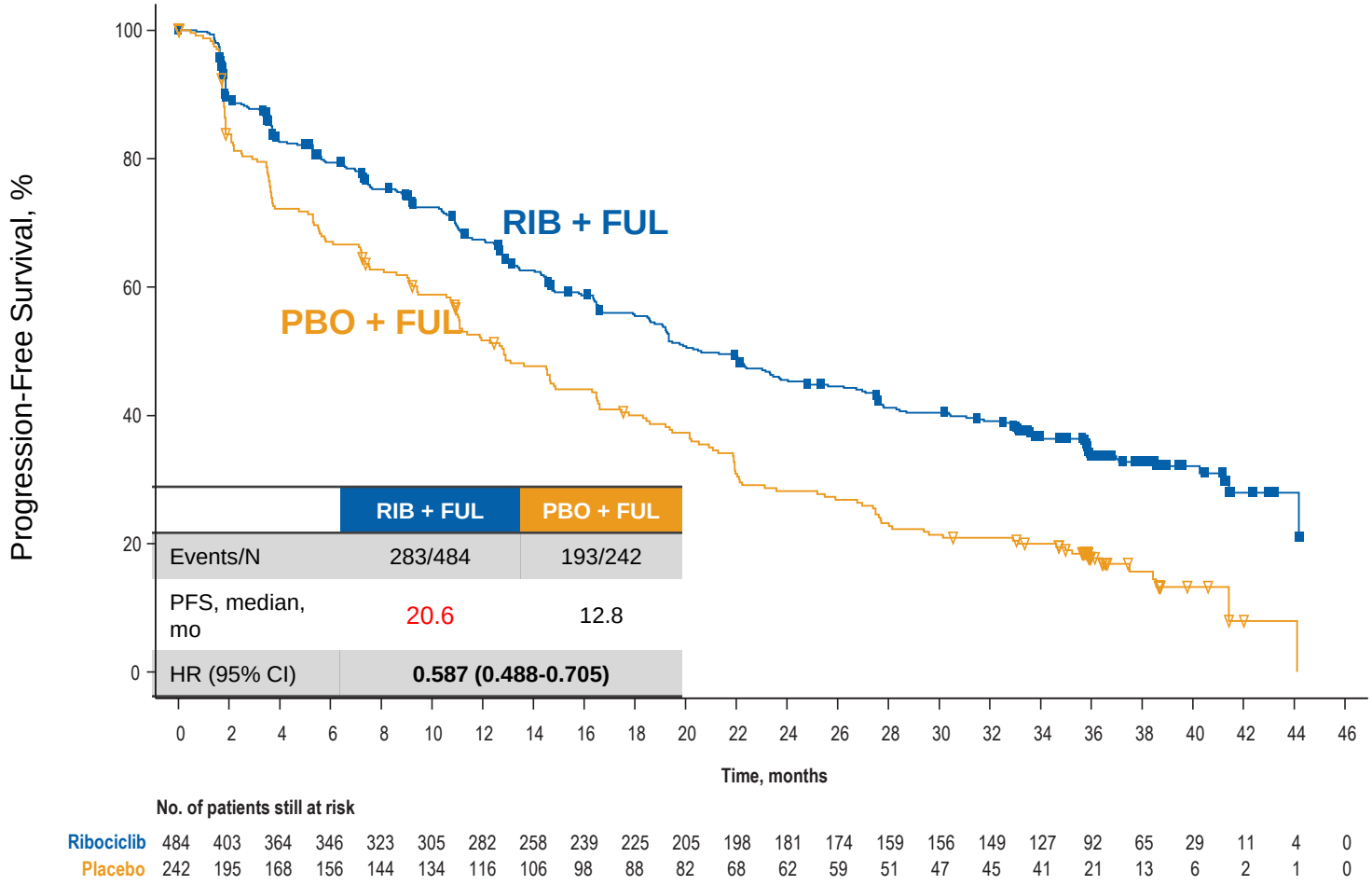


1L, first line; 2L, second line; ABC, advanced breast cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation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

[a] Fulvestrant 500 mg intramuscularly every 28 days plus an additional dose on Cycle 1, Day

Progression-Free Survival: Overall Population

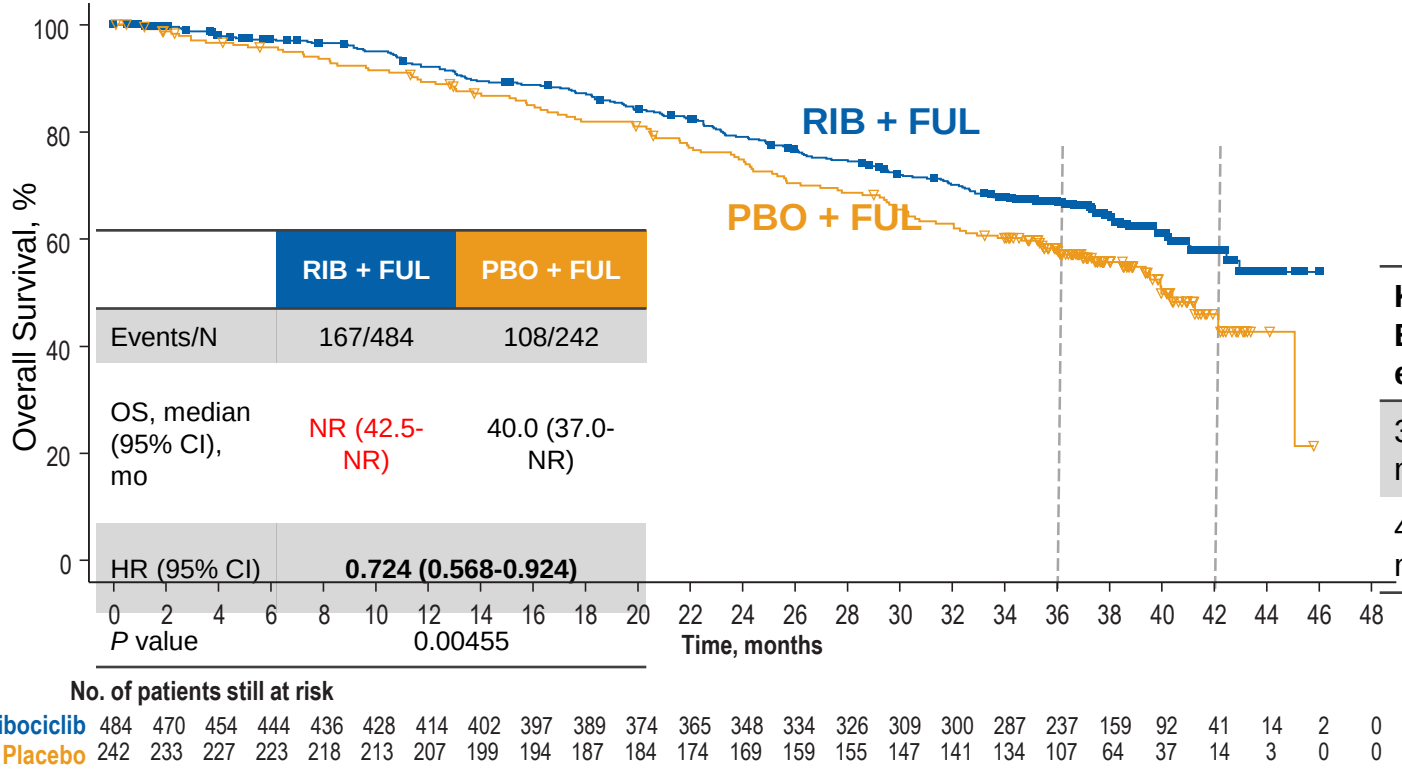
Descriptive analysis of PFS consistent with primary report



FUL, fulvestrant; HR, hazard ratio; PBO, placebo; PFS, progression-free survival; RIB, ribociclib.

Overall Survival

The reduction in relative 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	

Landmark Analysis

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

No. of patients still at risk

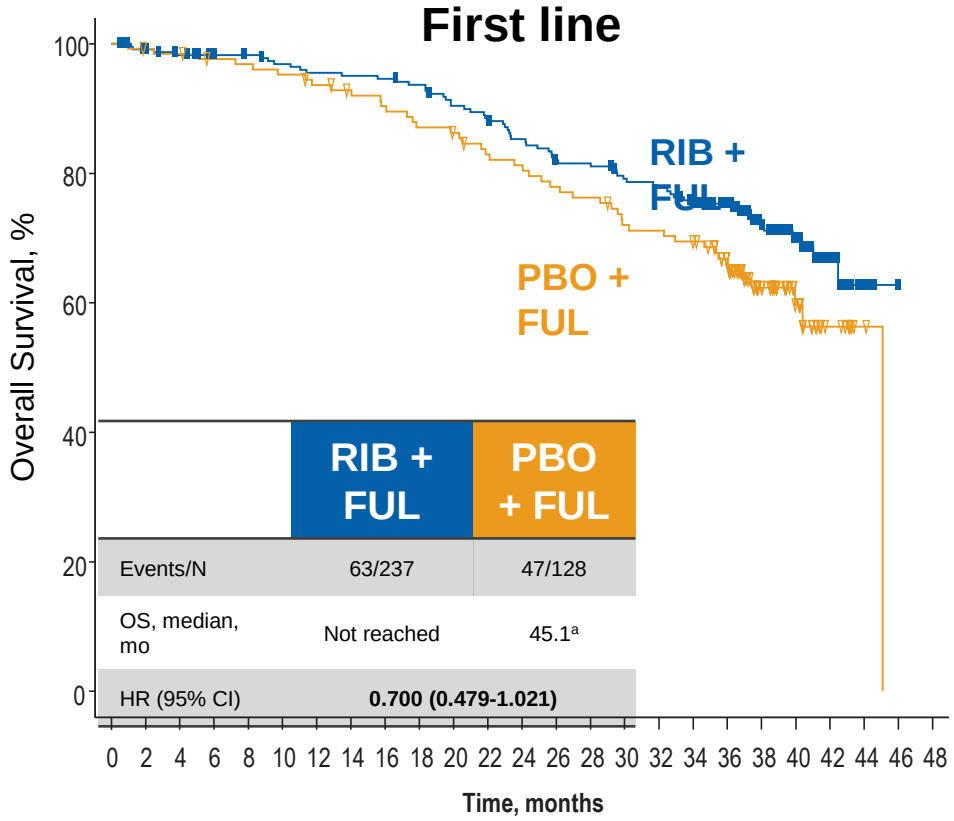
Ribociclib	484	470	454	444	436	428	414	402	397	389	374	365	348	334	326	309	300	287	237	159	92	41	14	2	0
Placebo	242	233	227	223	218	213	207	199	194	187	184	174	169	159	155	147	141	134	107	64	37	14	3	0	0

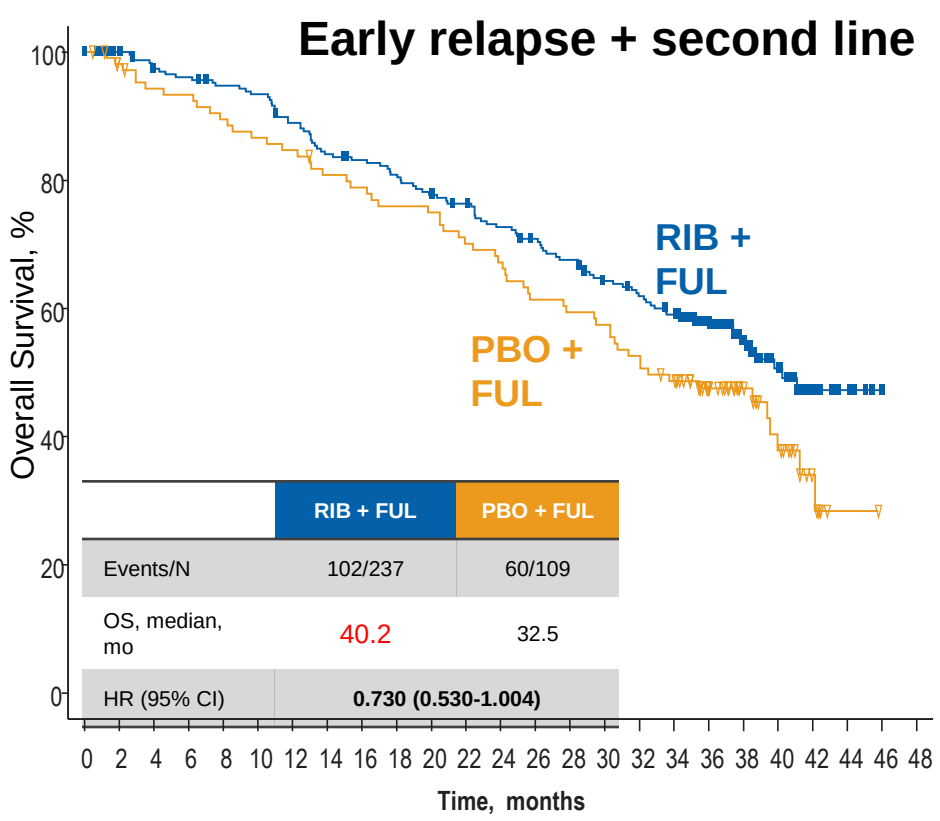
- The *P* value of 0.00455 crossed the prespecified boundary to claim superior efficacy (*P* < 0.01129)

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

Overall Survival by Line of Therapy

OS by line of therapy was consistent with overall population





No. of patients still at risk

Ribociclib	237	229	222	217	214	210	207	206	205	202	194	190	182	174	173	166	163	157	138	92	54	22	6	1	0
Placebo	128	126	125	122	121	121	119	116	113	110	106	104	99	97	93	91	85	84	82	70	40	21	8	2	0

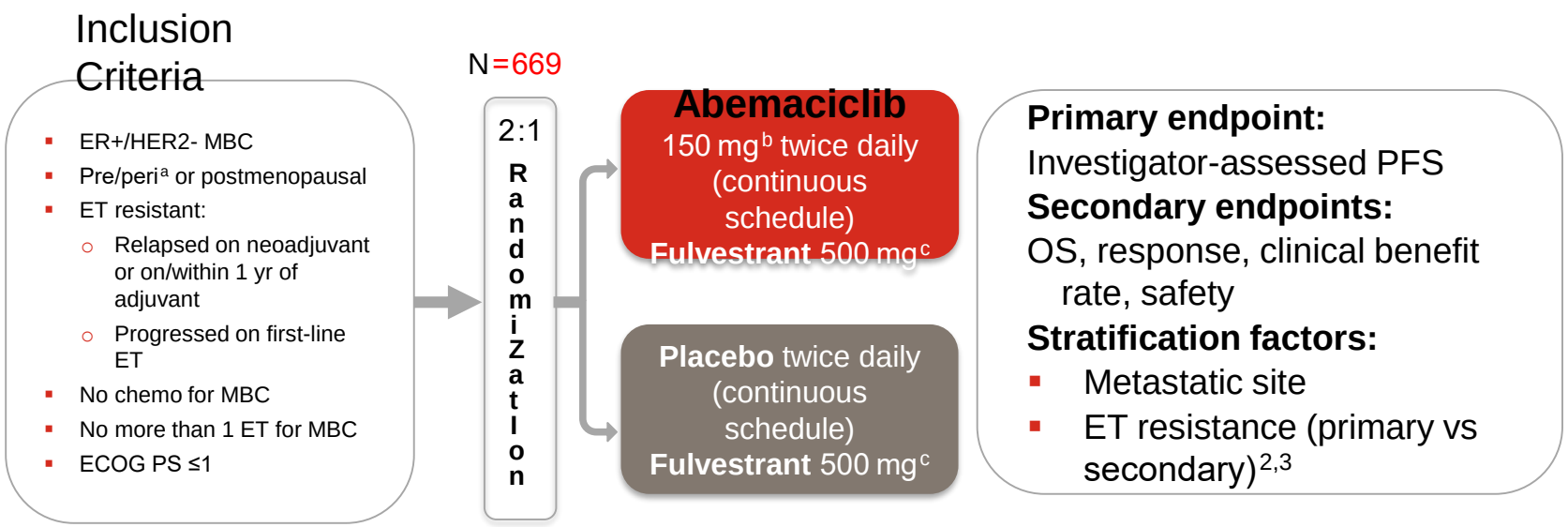
No. of patients still at risk

Ribociclib	237	231	222	218	213	210	199	188	184	179	172	167	158	152	145	135	129	122	94	63	36	17	7	1	0
Placebo	109	103	98	97	93	90	88	83	81	78	77	72	69	63	61	59	54	49	35	23	15	6	1	0	0

FUL, fulvestrant; HR, hazard ratio; OS, overall survival; PBO, placebo; RIB, ribociclib.

[a] This median value may not be estimated reliably due to the last patient on follow-up, who had an event at 45.1 months.

MONARCH 2: Study Design



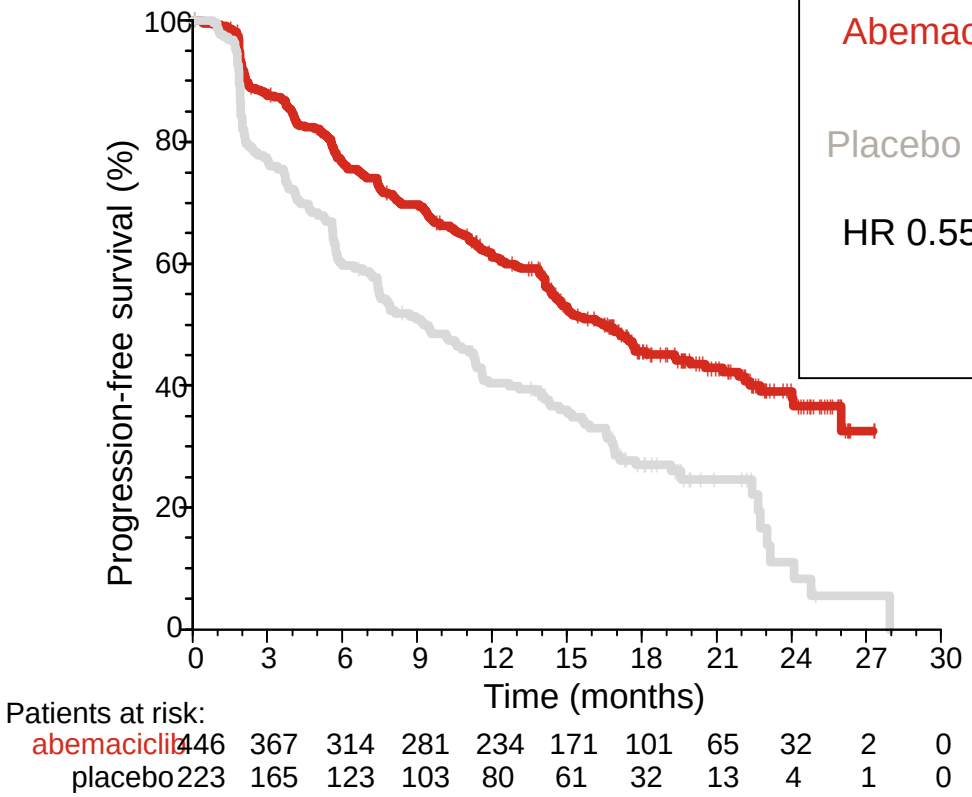
Study Population at Baseline[1]:

- Bone-only disease – 27%
- Visceral disease – 56%
- Primary ET resistance – 25%
- De novo metastatic – 20%

[a]Required to receive GnRH agonist; [b]Dose reduced by protocol amendment in all new and ongoing patients from 200 mg to 150 mg twice daily after 178 patients enrolled; 121 were randomized to abemaciclib at the 200 mg starting dose and 57 to matching placebo[3]; [c]Fulvestrant administered per label.

1. Sledge GW, *et al*. J Clin Oncol 2017; 35:2875-2884 2. Cardoso F, *et al. Breast* 2014;6:489–502; 3. Cardoso F, *et al. Ann Oncol* 2014;25:1871–88.

MONARCH 2: Primary Endpoint, PFS (ITT)



Median PFS

Abemaciclib + fulvestrant: 16.4 months

Placebo + fulvestrant: 9.3 months

HR 0.553 (95%CI 0.449, 0.681)

p<0.0000001

PFS benefit confirmed by blinded independent central review [HR 0.460 (95% CI 0.363, 0.584) p<0.000001]

Gráfica adaptada de: Sledge GW Jr, *et al*. *J Clin Oncol* 2017;35:2875–84

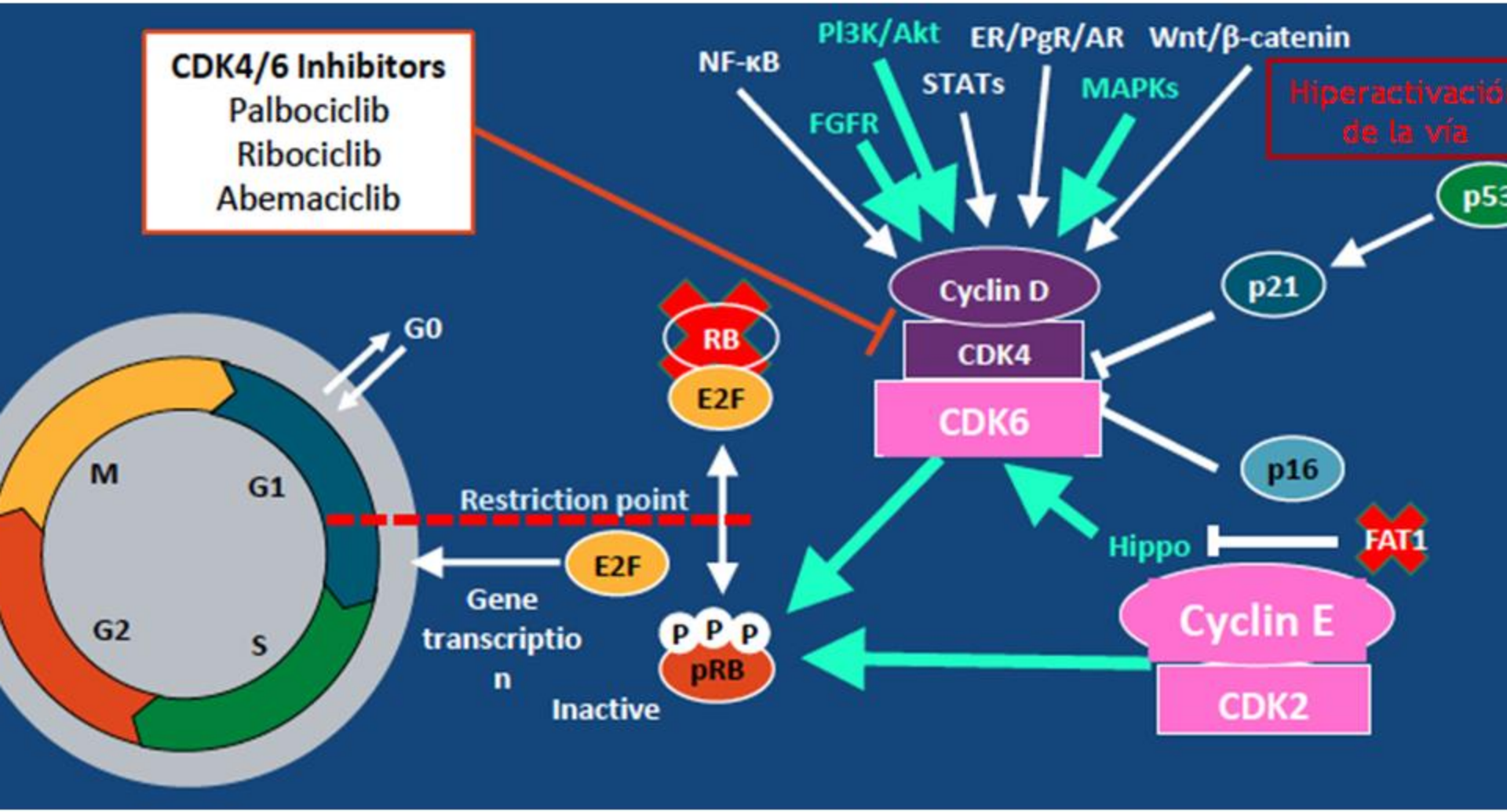
Sledge GW Jr, *et al. J Clin Oncol* 2017;35:2875–84.

Efectos adversos

-Muy bien tolerados

-Neutropenias (afebriles) transitorias

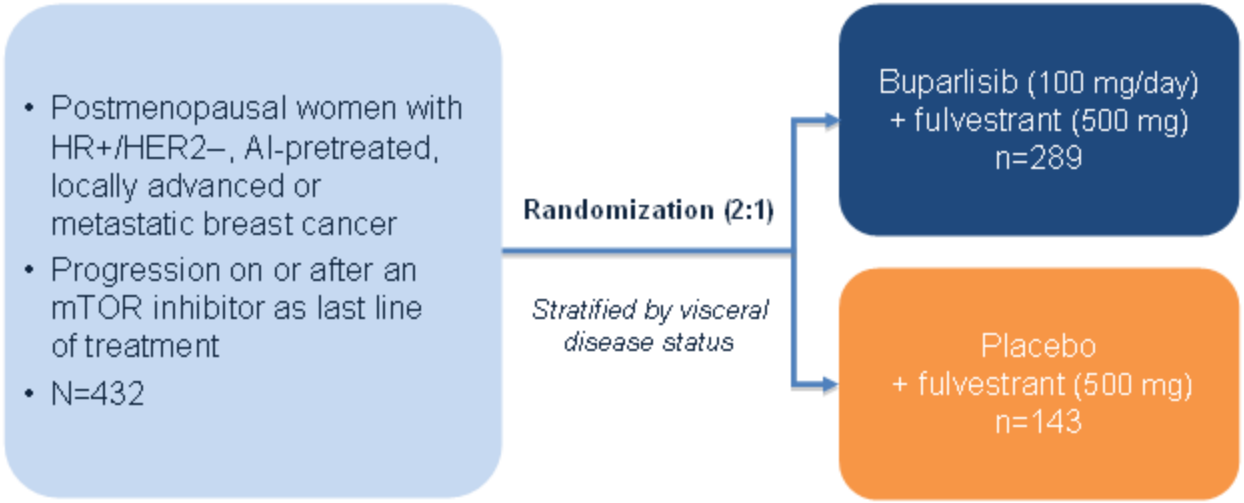
Terapias del Futuro



Adaptado

¿Hormonoterapia tras PE a inhibidores de ciclinas?

BELLE-3 Study Design and Endpoints



- Tumor assessments were performed every 6 weeks
- 90% power to detect a 33% risk reduction in PFS (disease progression or death) at one-sided α=0.025, based on the observation of 313 PFS events

Primary endpoint
- PFS (locally assessed per RECIST v1.1)

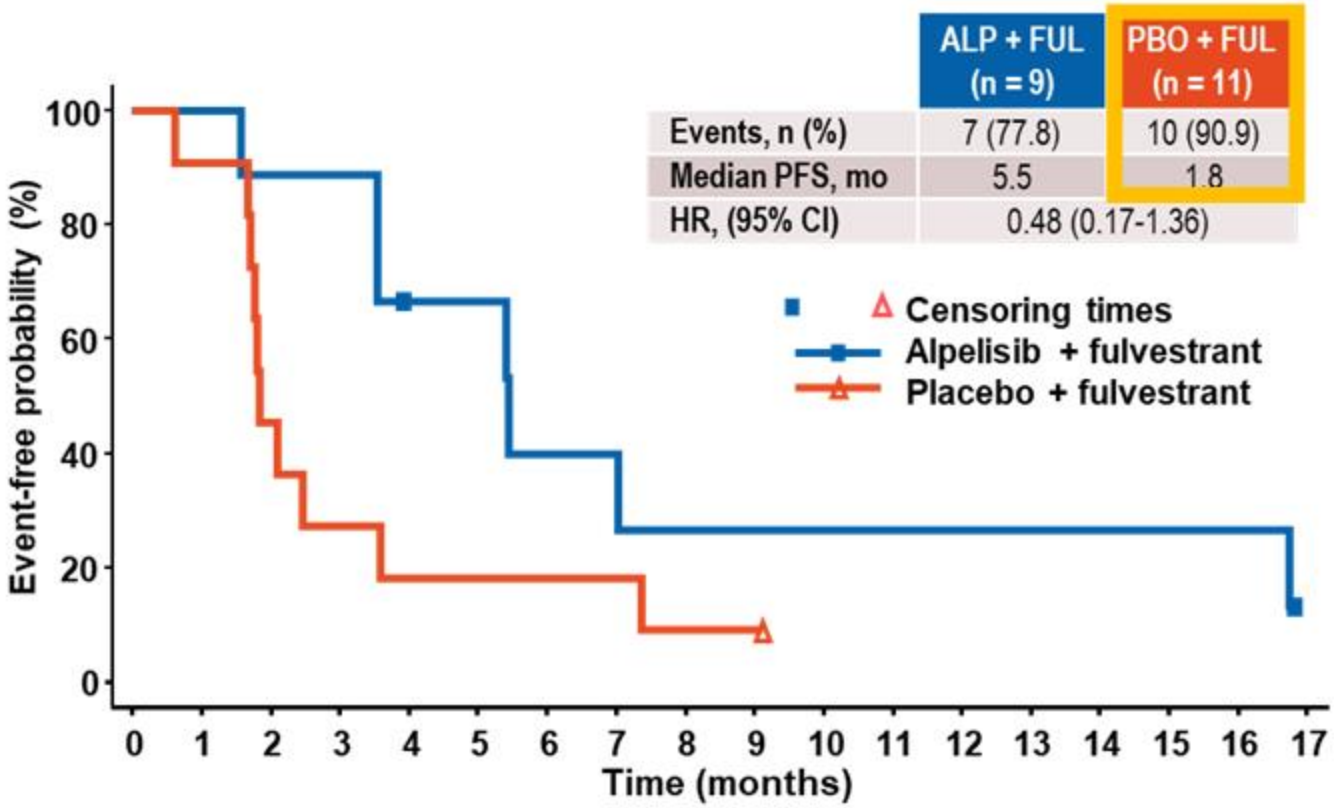
Key secondary endpoint
- OS

Other secondary endpoints
- PFS by *PIK3CA* status (ctDNA)
- OS by *PIK3CA* status (ctDNA)
- ORR and CBR in the full population and by *PIK3CA* status (ctDNA)
- Safety, pharmacokinetics, quality of life

¿Hormonoterapia tras PE a inhibidores de ciclinas?

Estudio SOLAR-1: Subgrupo pre-tto con Inh CDK 4/6

With Prior CDK4/6 inhibitor therapy



CONCLUSIONES

-Mejoría de SLP en todos los ensayos 1ª, 2ª y sucesivas

-SG en enfermedad refractaria

-Pre y post menopáusicas

-Magnifica tolerabilidad

-Estudios de calidad de vida muy favorables