INSTITUT RÉGIONAL FÉDÉRATIF DU CANCER
FRANCHE-COMTÉ
IRFC

7 de Abril del 2019

3° Taller Internacional Multidisciplinario de Cancer de Mama

Inhibidores de quinasas dependiente de ciclinas: Su posicionamiento en la secuencia hormonoterapica

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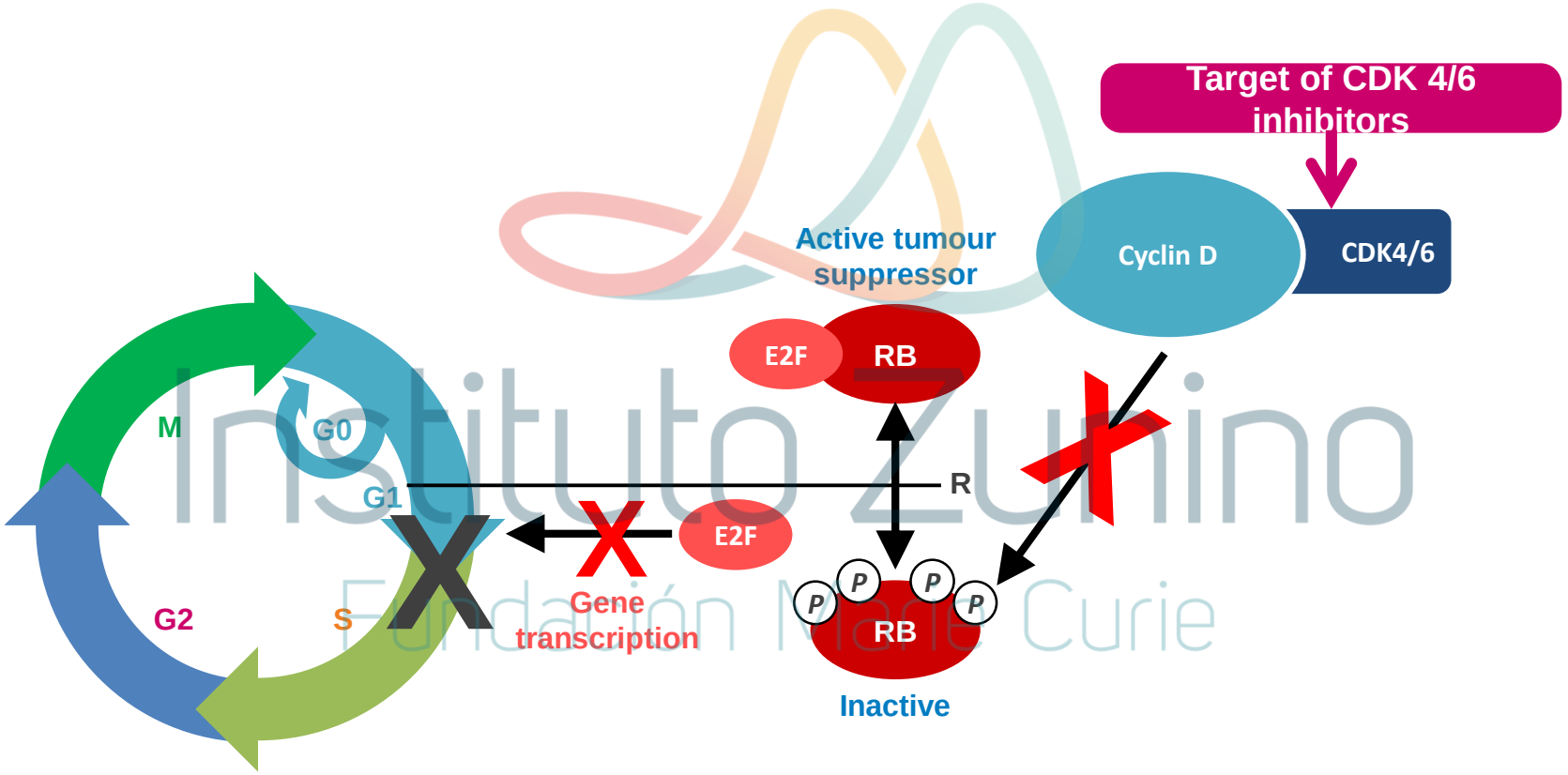
Conflicto de intereses

- Roche
- Astra-Zeneca
- Pfizer

Introduccion

- Cancer de Mama RH+ HER2- representa 70% de todos los tipos histologicos
- Hormonoterapia es el tratamiento de eleccion en presencia de metastasis, salvo en caso de crisis visceral.

Inhibidores de CDK 4/6: Mecanismo de accion



Fry DW, et al. Mol Cancer Ther. 2004;3:1427.
Carnero A. Br J Cancer. 2002;87:129.

Inhibidores de CDK 4/6

Palbociclib (PD0332991)	Ribociclib (LEE011)	Abemaciclib (LY28335219)
Pfizer	Novartis	Lilly
PALOMA	MONALEESA	MONARCH

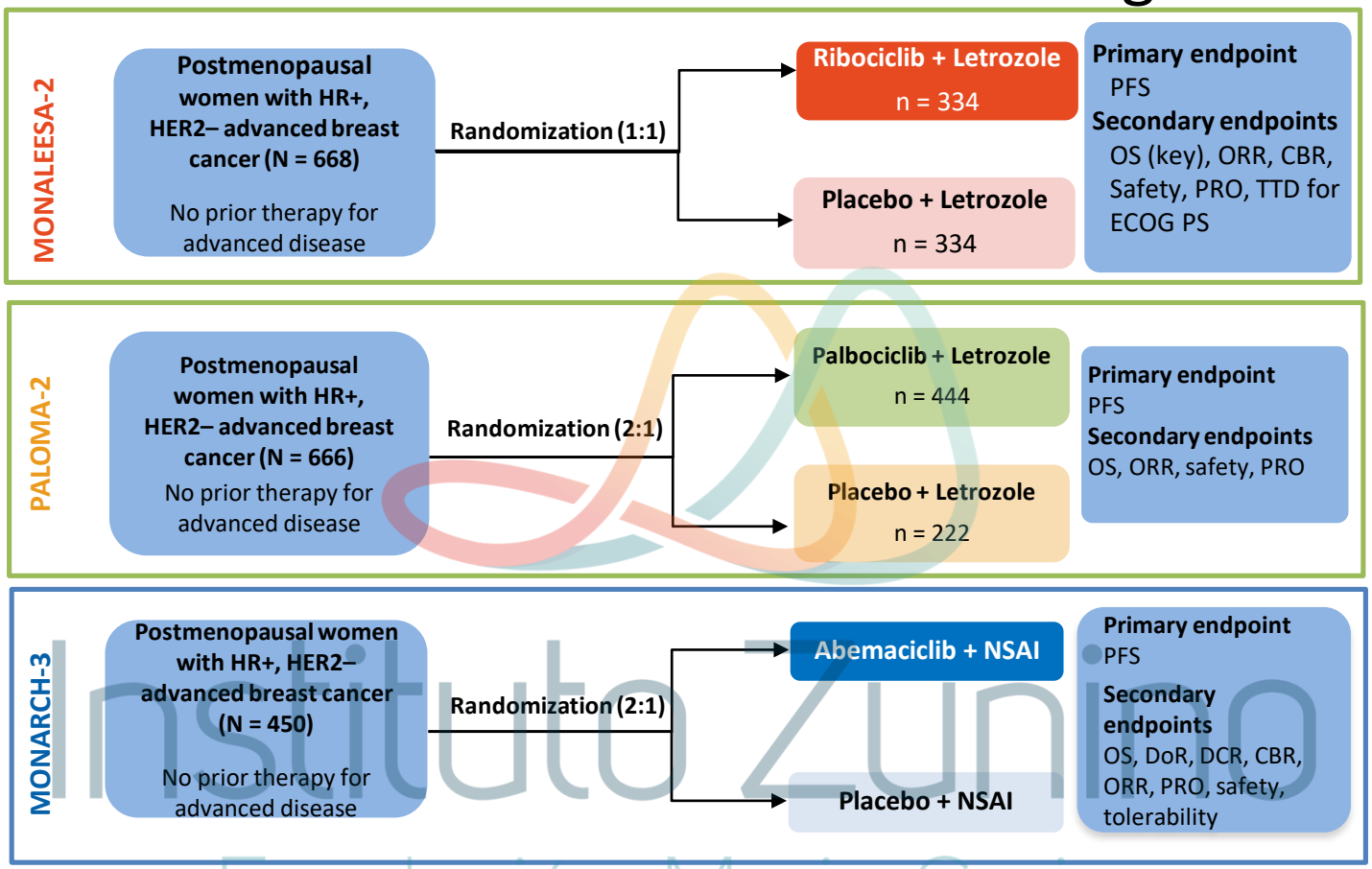
Clinicaltrials.gov. Palbociclib: NCT01740427; Ribociclib : NCT01958021; Abemaciclib: NCT02057133.

- 1° Linea

Instituto Zunino

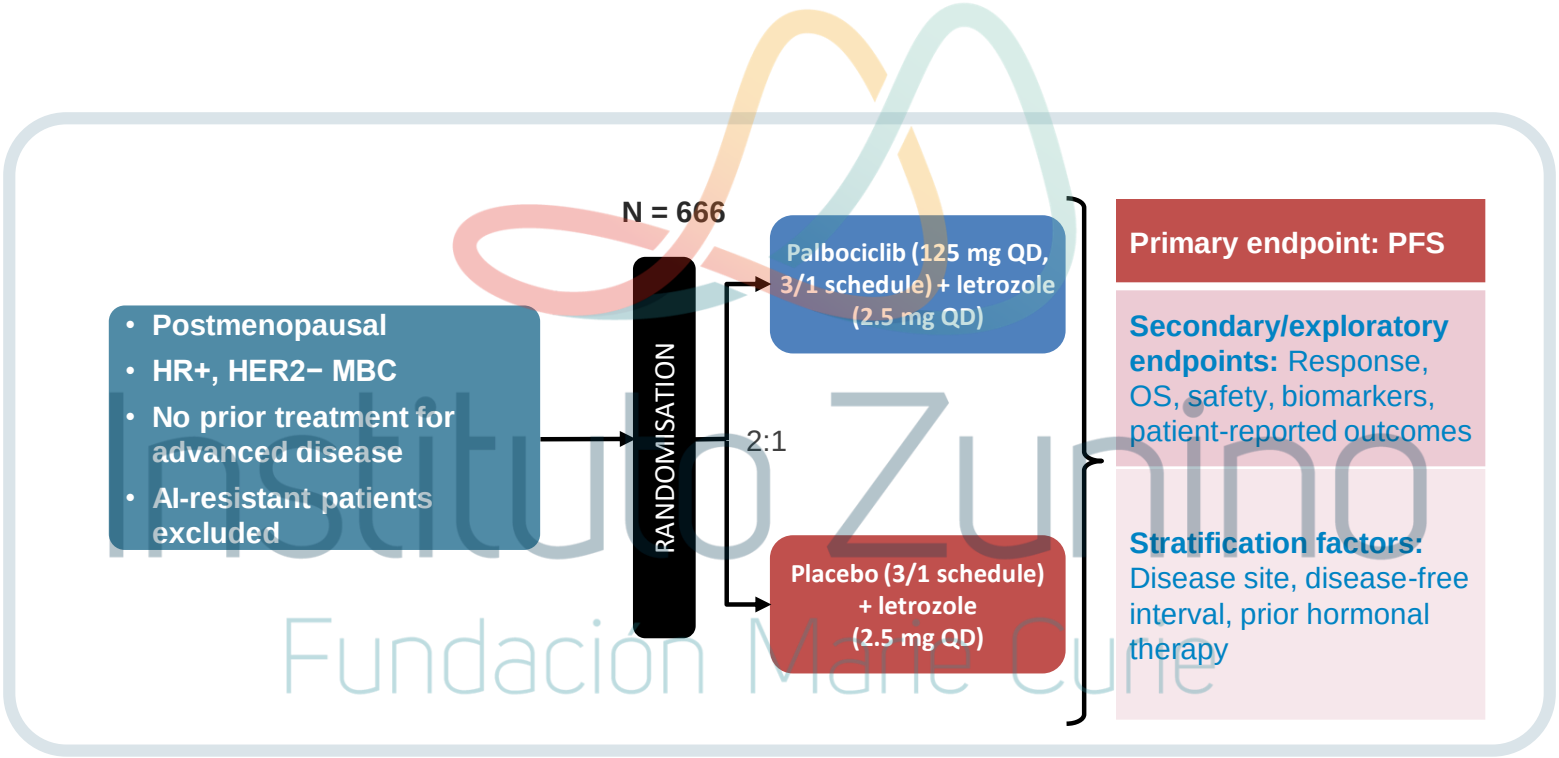
Fundación Marie Curie

Clinical trials in the first-line setting



CBR, clinical benefit rate; DCR, disease control rate; DoR, duration of response; EDoCB, expected duration of clinical benefit; EDoR, expected duration of response; OS, overall survival; ORR, overall response rate; PFS, progression-free survival; PRO, patient-reported outcome; TTD, time to deterioration.

PALOMA-2



Finn et al. NEJM 2016; 375; 20

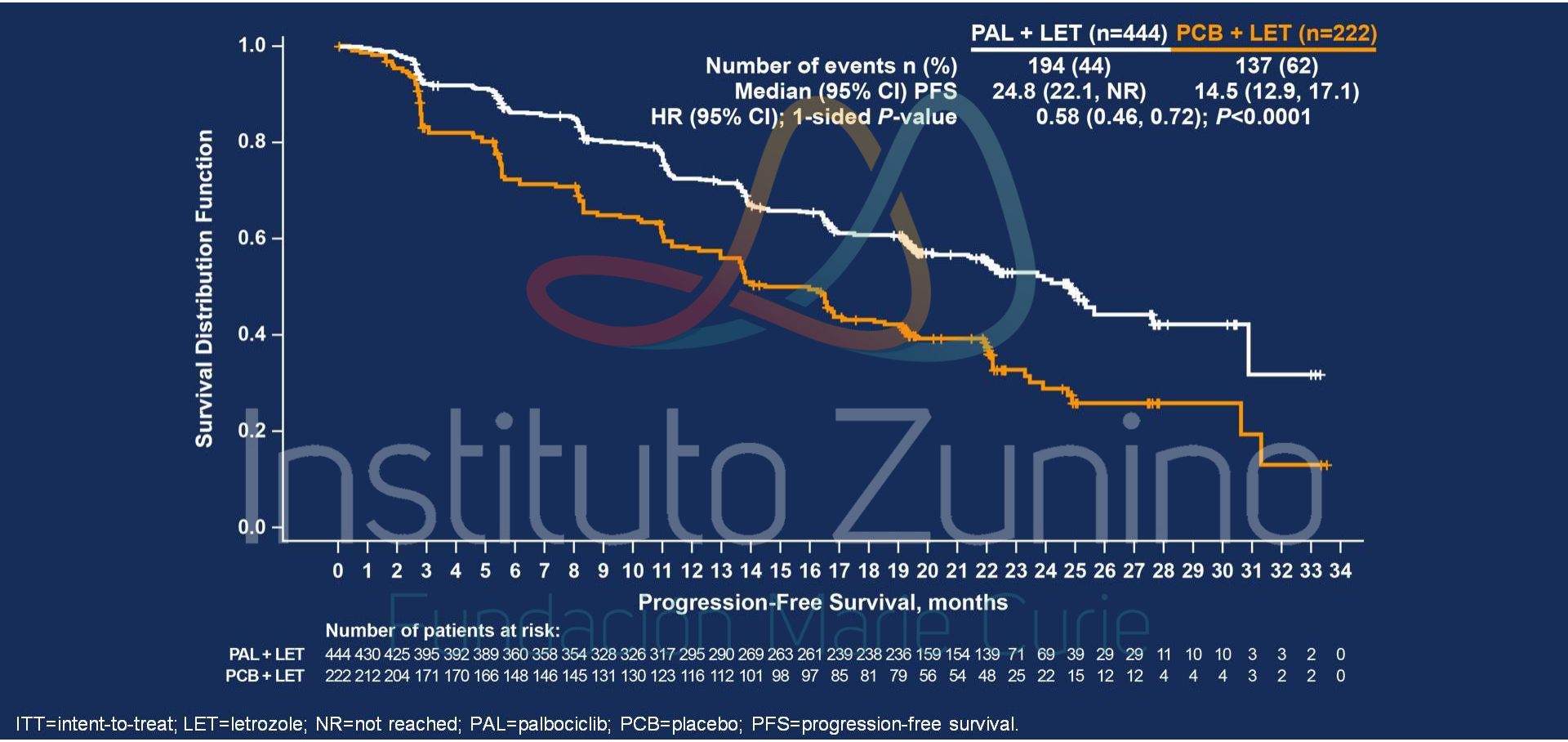
Paloma 2: caracteristicas de los pacientes

Table 1. Patient Demographic and Clinical Characteristics.*

Characteristic	Palbociclib–Letrozole (N = 444)	Placebo–Letrozole (N = 222)
Age		
Median (range) — yr	62 (30–89)	61 (28–88)
<65 yr — no. (%)	263 (59.2)	141 (63.5)
≥65 yr — no. (%)	181 (40.8)	81 (36.5)
Race — no. (%)†		
White	344 (77.5)	172 (77.5)
Asian	65 (14.6)	30 (13.5)
Black	8 (1.8)	3 (1.4)
Other	27 (6.1)	17 (7.7)
ECOG performance status — no. (%)‡		
0	257 (57.9)	102 (45.9)
1	178 (40.1)	117 (52.7)
2	9 (2.0)	3 (1.4)
Disease stage at initial diagnosis — no. (%)		
I	51 (11.5)	30 (13.5)
II	137 (30.9)	68 (30.6)
III	72 (16.2)	39 (17.6)
IV	138 (31.1)	72 (32.4)
Unknown	36 (8.1)	12 (5.4)
Other or data missing§	10 (2.3)	1 (0.5)
Recurrence type — no. (%)		
Locoregional	2 (0.5)	2 (0.9)
Local	6 (1.4)	3 (1.4)
Regional	3 (0.7)	1 (0.5)
Distant	294 (66.2)	145 (65.3)
Newly diagnosed	139 (31.3)	71 (32.0)
Disease-free interval — no. (%)¶		
Newly metastatic disease	167 (37.6)	81 (36.5)
≤12 mo	99 (22.3)	48 (21.6)
>12 mo	178 (40.1)	93 (41.9)
Disease site — no. (%)		
Visceral	214 (48.2)	110 (49.5)
Nonvisceral	230 (51.8)	112 (50.5)
Bone only	103 (23.2)	48 (21.6)
No. of disease sites — no. (%)		
1	138 (31.1)	66 (29.7)
2	117 (26.4)	52 (23.4)
3	112 (25.2)	61 (27.5)
≥4	77 (17.3)	43 (19.4)

Finn et al. NEJM 2016; 375; 20

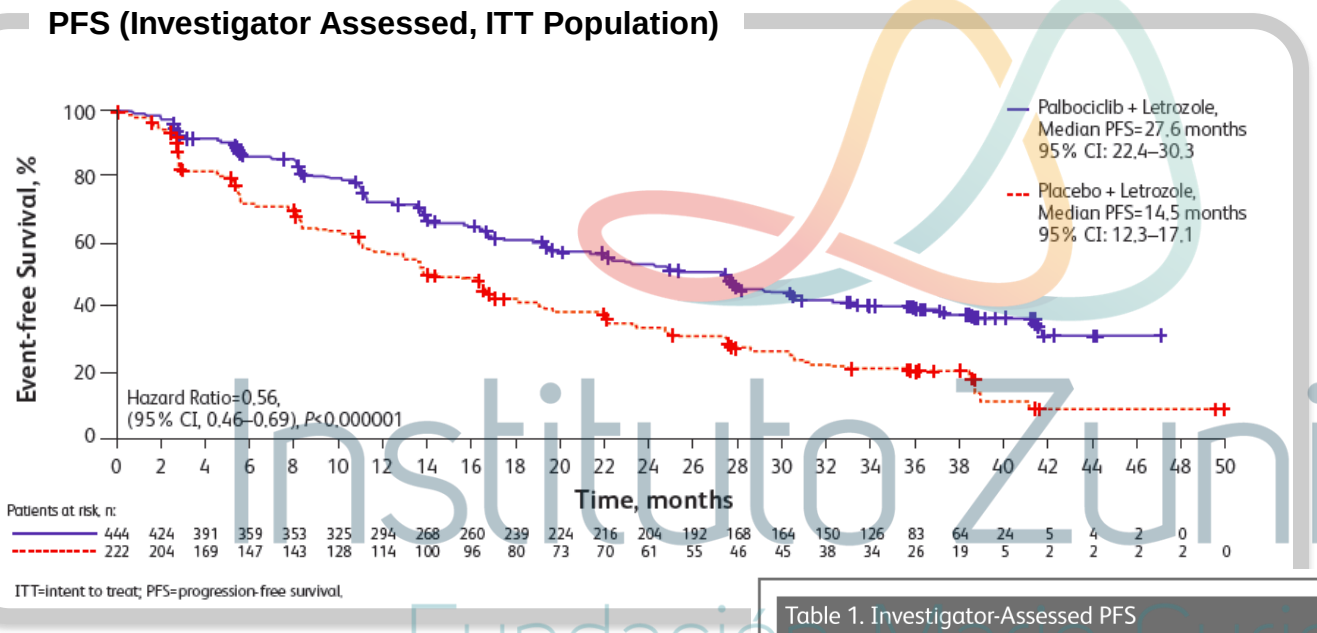
PALOMA-2: PFS Investigator-assessed (ITT)



ITT=intent-to-treat; LET=letrozole; NR=not reached; PAL=palbociclib; PCB=placebo; PFS=progression-free survival.

Finn et al. NEJM 2016; 375; 20

PALOMA-2 : actualizacion



- Follow up: 37 meses
- PFS : 27,6 m palbo + let *vs* 14,5 m Letro
- HR = 0,563

Table 1. Investigator-Assessed PFS

	Data Cutoff Date: February 26, 2016*		Data Cutoff Date: May 31, 2017†	
	Palbociclib + Letrozole	Placebo + Letrozole	Palbociclib + Letrozole	Placebo + Letrozole
Median PFS, mo (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); 1-sided *P* value	0.576 (0.463–0.718); *P*<0.000001		0.563 (0.461–0.687); *P*<0.000001	

HR=hazard ratio; NE=not estimable; PFS=progression-free survival
*Median follow-up duration was 23.0 months in the palbociclib + letrozole arm and 22.3 months in the placebo + letrozole arm.
†Median follow-up duration was 37.6 months in the palbociclib + letrozole arm and 37.3 months in the placebo + letrozole arm.

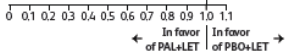
Rugo et al. Breast Cancer Research and Treatment (2019); 174:719

PFS: analisis de subgrupos

- PFS prolongada en todos los grupos
- Sin impacto DFI sobre la PFS

Figure 2. Forest Plot of Progression-Free Survival – Overall and Subgroup Analysis (IA, ITT)

Baseline Factors	PAL+LET Patients, n (%)	PBO+LET Patients, n (%)	PAL+LET mPFS (95% CI)	PBO+LET mPFS (95% CI)	PAL+LET vs PBO+LET HR (95% CI)	P*
All randomized patients, IA	444 (100)	222 (100)	27,6 (22,4–30,3)	14,5 (12,3–17,1)	0,56 (0,46–0,69)	<0,0001
All randomized patients, BICR	444 (100)	222 (100)	35,7 (27,7–38,9)	19,5 (16,6–26,6)	0,61 (0,49–0,77)	<0,0001
Visceral disease	214 (48,2)	110 (49,5)	19,3 (16,4–24,2)	12,3 (8,4–16,4)	0,62 (0,47–0,81)	<0,0005
Nonvisceral disease	230 (51,8)	112 (50,5)	35,9 (27,7–NE)	17,0 (13,8–24,8)	0,50 (0,37–0,67)	<0,0001
Bone-only disease	103 (23,2)	48 (21,6)	36,2 (27,6–NE)	11,2 (8,2–22,0)	0,41 (0,26–0,63)	<0,0001
No bone-only disease[†]	341 (76,8)	174 (78,4)	24,2 (19,4–27,7)	14,5 (12,9–18,5)	0,62 (0,50–0,78)	<0,0001
DFI[‡] >12 mo	179 (40,3)	93 (41,9)	30,3 (24,8–NE)	13,8 (8,8–18,2)	0,55 (0,40–0,76)	<0,0005
DFI[‡] ≤12 mo	98 (22,1)	48 (21,6)	16,6 (13,9–24,2)	11,0 (5,6–12,9)	0,48 (0,32–0,72)	<0,0005
DFI[‡] >2 y	154 (34,7)	77 (34,7)	38,5 (27,5–NE)	16,6 (13,7–23,5)	0,52 (0,36–0,75)	<0,0005
DFI[‡] >5 y	90 (20,3)	46 (20,7)	38,6 (27,6–NE)	23,5 (16,3–32,2)	0,60 (0,36–1,00)	<0,05
DFI[‡] >10 y	32 (7,2)	23 (10,4)	NR (30,4–NE)	23,5 (16,6–NE)	0,44 (0,19–1,03)	<0,05
De novo metastatic	167 (37,6)	81 (36,5)	27,9 (22,1–33,4)	22,0 (13,9–27,4)	0,61 (0,44–0,85)	<0,005
DFI from prior ET >12 mo	156 (35,1)	78 (35,1)	27,6 (22,2–38,6)	13,8 (8,2–16,6)	0,58 (0,41–0,82)	<0,001
DFI from prior ET ≤12 mo	94 (21,2)	48 (21,6)	16,6 (13,9–24,2)	11,0 (5,6–12,9)	0,49 (0,33–0,73)	<0,0005
Measurable disease	338 (76,1)	171 (77,0)	23,7 (19,3–27,6)	14,5 (12,3–18,5)	0,63 (0,50–0,79)	<0,0001
Nonmeasurable disease[§]	106 (23,9)	51 (23,0)	36,2 (27,6–NE)	16,5 (8,3–19,6)	0,39 (0,25–0,60)	<0,0001
No prior ET with visceral disease	86 (19,4)	47 (21,2)	23,7 (16,8–30,3)	13,9 (10,2–22,2)	0,55 (0,36–0,85)	<0,005
No prior ET without visceral disease	108 (24,3)	49 (22,1)	36,2 (27,9–NE)	27,6 (19,1–35,6)	0,59 (0,38–0,92)	<0,01
Prior ET	250 (56,3)	126 (56,8)	24,2 (18,8–27,6)	11,2 (8,4–14,5)	0,54 (0,42–0,71)	<0,0001
No prior ET	194 (43,7)	96 (43,2)	30,3 (24,5–35,7)	21,9 (15,9–27,4)	0,59 (0,43–0,80)	<0,0005
Prior chemotherapy	213 (48,0)	109 (49,1)	24,8 (19,3–27,9)	12,9 (9,6–16,5)	0,53 (0,40–0,71)	<0,0001
No prior chemotherapy	231 (52,0)	113 (50,9)	27,9 (23,2–33,4)	18,5 (13,6–24,8)	0,59 (0,45–0,79)	<0,0005
Disease site, 1	138 (31,1)	66 (29,7)	30,4 (24,8–NE)	16,5 (11,0–22,1)	0,52 (0,36–0,75)	<0,0005
Disease sites, 2	117 (26,4)	52 (23,4)	28,1 (19,4–NE)	16,3 (11,0–27,4)	0,57 (0,37–0,89)	<0,01
Disease sites, ≥3	189 (42,6)	104 (46,8)	23,7 (19,2–27,6)	13,8 (8,8–17,0)	0,61 (0,46–0,82)	<0,0005
ECOG PS 0	257 (57,9)	102 (45,9)	27,9 (24,9–36,2)	19,3 (14,5–24,9)	0,65 (0,48–0,87)	<0,005
ECOG PS 1/2	187 (42,1)	120 (54,1)	22,2 (16,6–27,7)	11,8 (8,3–16,5)	0,51 (0,39–0,68)	<0,0001
Age <65 y	263 (59,2)	141 (63,5)	23,2 (19,3–27,6)	13,7 (11,0–16,6)	0,55 (0,43–0,70)	<0,0001
Age ≥65 y	181 (40,8)	81 (36,5)	30,6 (27,6–NE)	19,1 (11,0–30,4)	0,60 (0,43–0,86)	<0,005



BICR=blinded independent central review; DFI=disease-free interval; ECOG PS=Eastern Cooperative Oncology Group performance status; ET=endocrine therapy; HR=hazard ratio; IA=investigator assessed; ITT=intent to treat; LET=letrozole; mPFS=median progression-free survival; NE=not estimable; NR=not reached; PAL=palbociclib; PBO=placebo.

*1-sided *P* value from the log-rank test.

†Per tumor site.

‡Protocol-defined DFI refers to DFI since completion of prior (neo)adjuvant therapy and onset of metastatic disease or disease recurrence.

§A few patients initially enrolled as having measurable disease were later found to have nonmeasurable disease beyond bone-only disease.

Rugo et al. Breast Cancer Research and Treatment (2019); 174:719

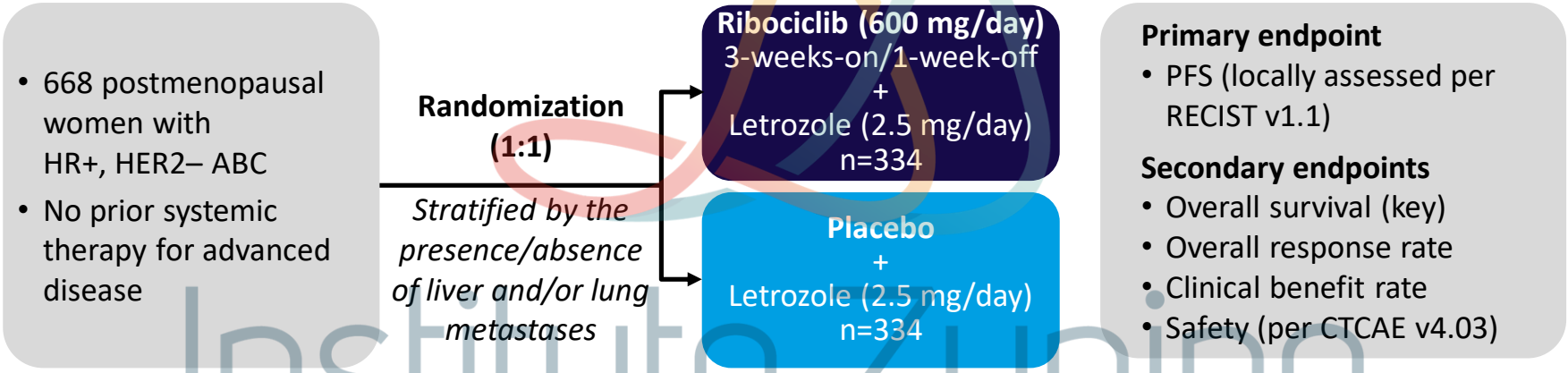
Efectos Secundarios

Table 2. Adverse Events from Any Cause That Occurred in at Least 10% of the Patients in Either Study Group in the As-Treated Population.

Adverse Event	Palbociclib–Letrozole (N = 444)			Placebo–Letrozole (N = 222)*		
	Any Grade	Grade 3	Grade 4†	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	439 (98.9)	276 (62.2)	60 (13.5)	212 (95.5)	49 (22.1)	5 (2.3)
Neutropenia‡	353 (79.5)	249 (56.1)	46 (10.4)	14 (6.3)	2 (0.9)	1 (0.5)
Leukopenia§	173 (39.0)	107 (24.1)	3 (0.7)	5 (2.3)	0	0
Fatigue	166 (37.4)	8 (1.8)	0	61 (27.5)	1 (0.5)	0
Nausea	156 (35.1)	1 (0.2)	0	58 (26.1)	4 (1.8)	0
Arthralgia	148 (33.3)	3 (0.7)	0	75 (33.8)	1 (0.5)	0
Alopecia¶	146 (32.9)	0	0	35 (15.8)	0	0
Diarrhea	116 (26.1)	6 (1.4)	0	43 (19.4)	3 (1.4)	0
Cough	111 (25.0)	0	0	42 (18.9)	0	0
Anemia‖	107 (24.1)	23 (5.2)	1 (0.2)	20 (9.0)	4 (1.8)	0
Back pain	96 (21.6)	6 (1.4)	0	48 (21.6)	0	0
Headache	95 (21.4)	1 (0.2)	0	58 (26.1)	4 (1.8)	0
Hot flush	93 (20.9)	0	0	68 (30.6)	0	0
Constipation	86 (19.4)	2 (0.5)	0	34 (15.3)	1 (0.5)	0
Rash**	79 (17.8)	4 (0.9)	0	26 (11.7)	1 (0.5)	0
Asthenia	75 (16.9)	10 (2.3)	0	26 (11.7)	0	0
Thrombocytopenia††	69 (15.5)	6 (1.4)	1 (0.2)	3 (1.4)	0	0
Vomiting	69 (15.5)	2 (0.5)	0	37 (16.7)	3 (1.4)	0
Pain in extremity	68 (15.3)	1 (0.2)	0	39 (17.6)	3 (1.4)	0
Stomatitis	68 (15.3)	1 (0.2)	0	13 (5.9)	0	0
Decreased appetite	66 (14.9)	3 (0.7)	0	20 (9.0)	0	0
Dyspnea	66 (14.9)	5 (1.1)	0	30 (13.5)	3 (1.4)	0
Insomnia	66 (14.9)	0	0	26 (11.7)	0	0
Dizziness	63 (14.2)	2 (0.5)	0	33 (14.9)	0	0
Nasopharyngitis	62 (14.0)	0	0	22 (9.9)	0	0
Upper respiratory tract infection	59 (13.3)	0	0	25 (11.3)	0	0
Dry skin	55 (12.4)	0	0	13 (5.9)	0	0
Pyrexia	55 (12.4)	0	0	19 (8.6)	0	0

Finn et al. NEJM 2016; 375; 18

MONALEESA-2



- Tumor assessments were performed every 8 weeks for the first 18 months, then every 12 weeks thereafter
- Supportive PFS analyses were conducted in pre-specified patient subgroups including in patients aged <65 or ≥65 years

Hortobagyi et al. NEJM 2016; 375; 18

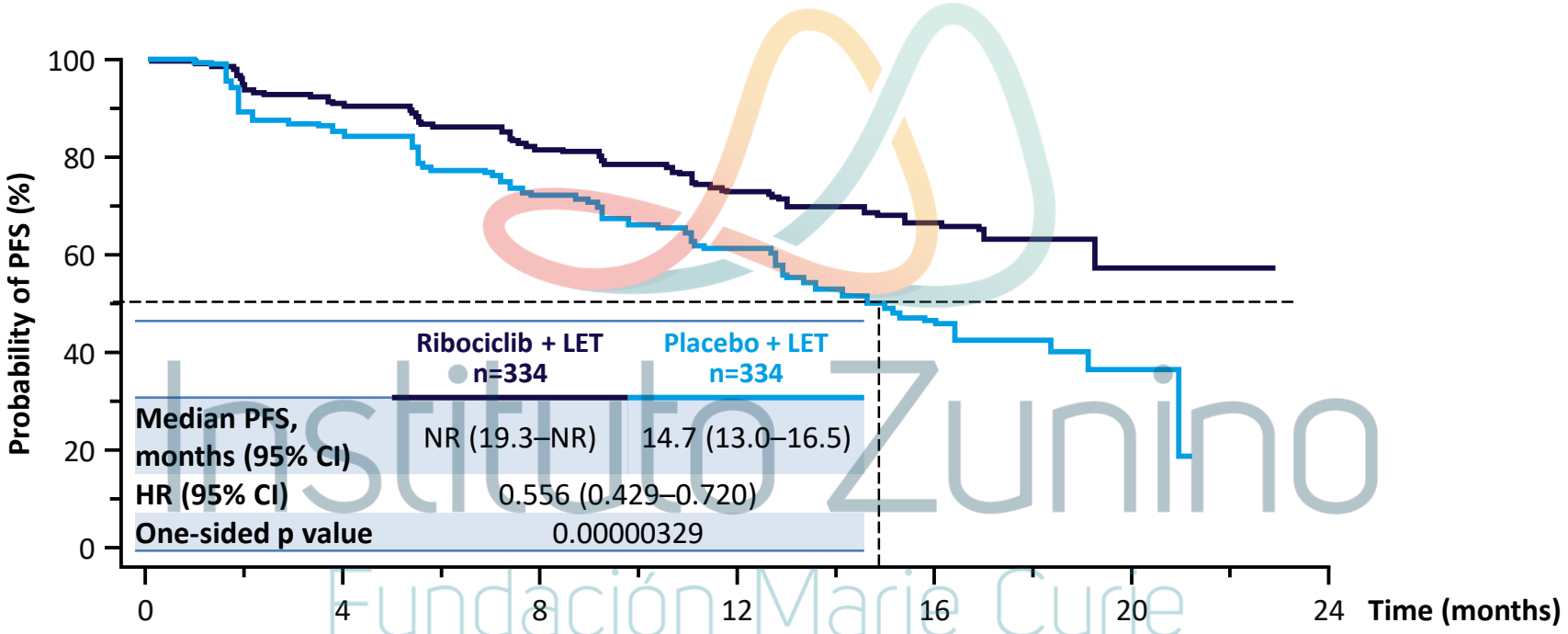
Caracteristicas de los pacientes

	Age <65 years (n=373)		Age ≥65 years (n=295)	
	Ribociclib + Letrozole n=184	Placebo + Letrozole n=189	Ribociclib + Letrozole n=150	Placebo + Letrozole n=145
Median age, years (range)	55 (23–64)	56 (29–64)	70 (65–91)	71 (65–88)
ECOG performance status, n (%)				
0	125 (68)	123 (65)	80 (53)	79 (55)
1	59 (32)	66 (35)	70 (47)	66 (46)
***De novo* ABC, n (%)**	60 (33)	61 (32)	54 (36)	52 (36)
Disease-free interval since end of (neo)adjuvant therapy, n (%)*				
≤12 months	3 (2)	6 (3)	1 (0.7)	4 (3)
>12 months	121 (66)	122 (65)	95 (63)	88 (61)
Metastatic sites, n (%)				
Bone-only disease	34 (18)	45 (24)	35 (23)	33 (23)
Visceral disease**	106 (58)	111 (59)	91 (61)	85 (59)
Number of metastatic sites, n (%)				
<3	122 (66)	130 (69)	98 (65)	91 (63)
≥3	62 (34)	59 (31)	52 (35)	54 (37)

ECOG, Eastern Cooperative Oncology Group.
*One patient age ≥65 years in the placebo + letrozole arm had an unknown disease-free interval;
**Includes liver, lung, and other visceral sites.

Hortobagyi et al. NEJM 2016; 375; 18

MONALEESA-2 : eficacia



- Treatment benefit was consistent for the secondary endpoints analyzed

Hortobagyi et al. NEJM 2016; 375; 18

Monaleesa 2: analisis de subgrupos

Subgroup	No. of Patients	HR (95% CI)
All patients	668	0.56 (0.43–0.72)
Age		
<65 yr	373	0.52 (0.38–0.72)
≥65 yr	295	0.61 (0.39–0.94)
Race		
Asian	51	0.39 (0.17–0.91)
Non-Asian	568	0.61 (0.46–0.80)
ECOG performance status		
1	407	0.59 (0.42–0.82)
0	261	0.53 (0.35–0.80)
Hormone-receptor status		
ER- and PR-positive	546	0.62 (0.46–0.82)
Other	122	0.36 (0.20–0.65)
Presence of liver or lung metastases		
No	295	0.55 (0.36–0.83)
Yes	373	0.57 (0.41–0.79)
Bone-only disease		
No	521	0.54 (0.41–0.72)
Yes	147	0.69 (0.38–1.25)
Newly diagnose disease		
No	441	0.60 (0.45–0.81)
Yes	227	0.45 (0.27–0.75)
Previous endocrine therapy		
NSAIs and others	53	0.45 (0.19–1.04)
Tamoxifen or exemestane	292	0.57 (0.39–0.83)
None	322	0.57 (0.38–0.85)
Previous chemotherapy		
No	377	0.55 (0.37–0.81)
Yes	291	0.55 (0.38–0.78)

Hortobagyi et al. N Engl J Med. 2016375(18):1738-1748

Hortobagyi et al. NEJM 2016; 375; 18

Efectos Secundarios

Adverse Event (≥25% of patients), n (%)	Age <65 years (n=370)		Age ≥65 years (n=294)	
	Ribociclib + Letrozole n=184	Placebo + Letrozole n=186*	Ribociclib + Letrozole n=150	Placebo + Letrozole n=144*
Neutropenia**	137 (75)	10 (5)	111 (74)	7 (5)
Nausea	92 (50)	52 (28)	80 (53)	42 (29)
Fatigue	67 (36)	64 (34)	55 (37)	35 (24)
Leukopenia‡	64 (35)	8 (4)	46 (31)	5 (4)
Alopecia	62 (33)	26 (14)	49 (33)	25 (17)
Diarrhea	56 (30)	36 (19)	61 (41)	37 (26)
Arthralgia	54 (29)	55 (30)	37 (25)	40 (28)
Hot flush	48 (26)	51 (27)	22(15)	27 (19)
Headache	47 (26)	42 (23)	27 (18)	21 (15)
Constipation	45 (25)	40 (22)	38 (25)	23 (16)
Vomiting	45 (25)	24 (13)	53 (35)	27 (19)
Anemia §	24 (13)	6 (3)	39 (26)	9 (6)

- All-grade liver enzyme elevations were reported in 19% vs 5% and 17% vs 6% of patients aged <65 years and ≥65 years (ribociclib vs placebo arm)
- In the ribociclib arm, one patient aged ≥65 years experienced Grade 3 prolonged QTcF (>500 ms)

All-grade adverse events reported in ≥25% of patients aged <65 or ≥65 years in the ribociclib + letrozole arm are presented.
QTcF, Fridericia's corrected QT interval.

Hortobagyi et al. NEJM 2016; 375; 18

Monaleesa 2: actualizacion

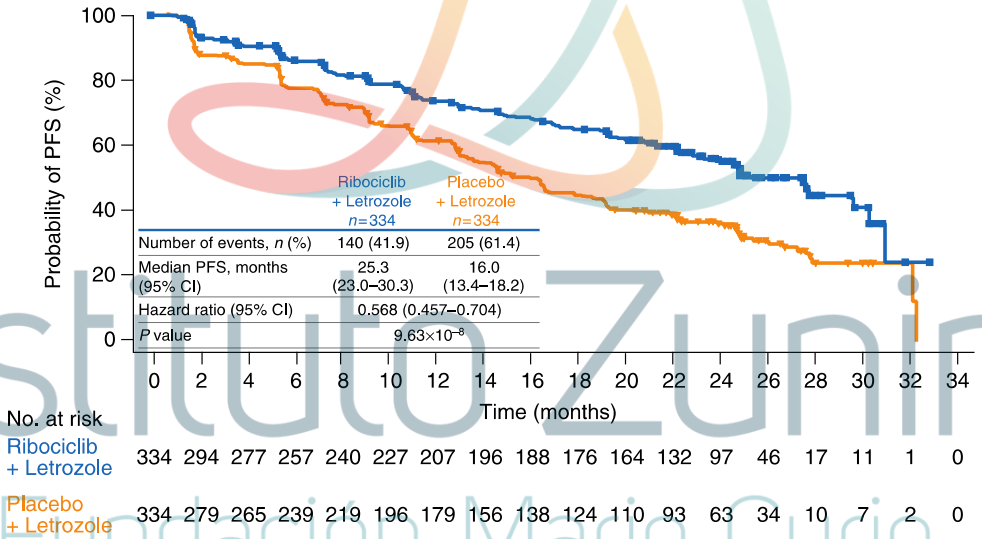
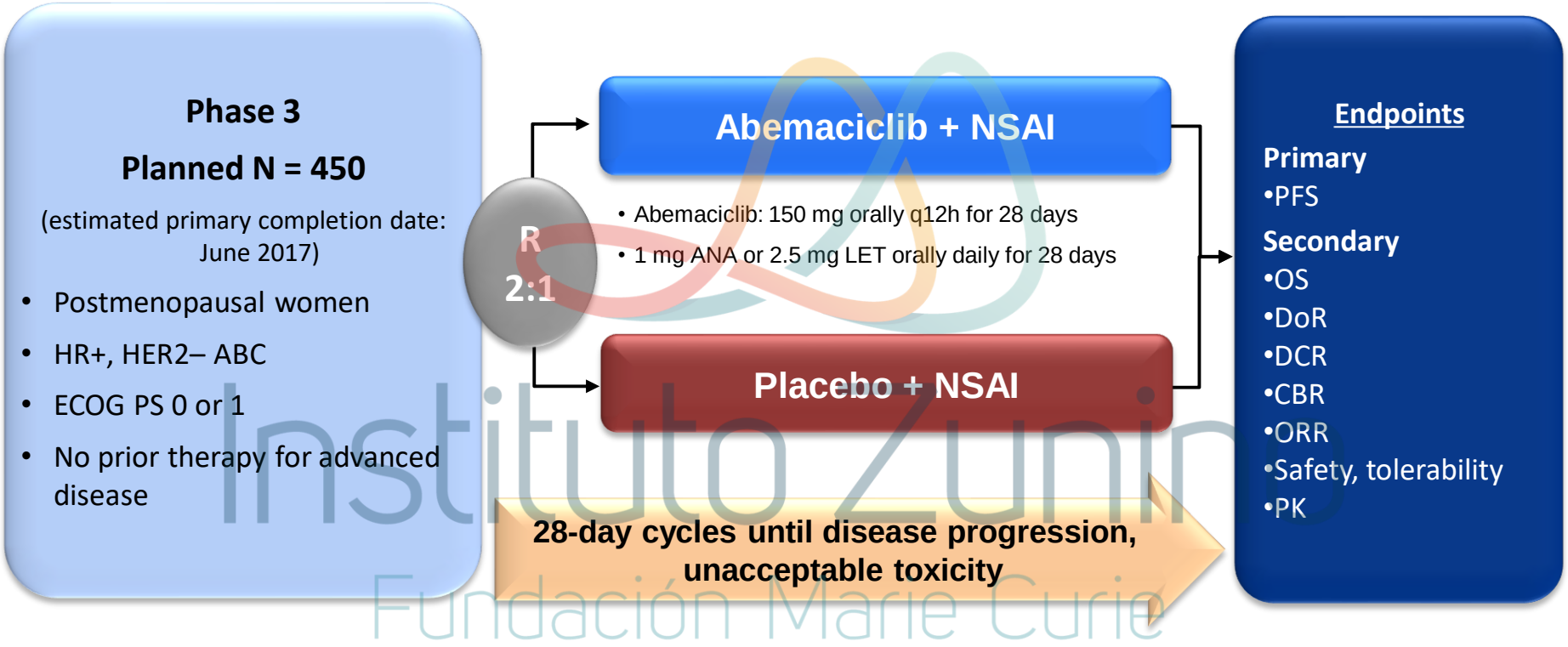


Figure 2. Kaplan–Meier graph of investigator-assessed PFS for ribociclib plus letrozole versus placebo plus letrozole. CI, confidence interval; PFS, progression-free survival. Data cut-off: 2 January 2017.

Hortobagyi et al. Annals of Oncology 2018; 29: 1541–1547

MONARCH-3



ABC, advanced breast cancer; ANA, anastrozole; CBR, clinical benefit rate; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2–, human epidermal growth factor receptor-2–negative; HR+, hormone receptor-positive; LET, letrozole; NSAI, nonsteroidal aromatase inhibitor; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; q12h, every 12 hours; R, randomization.

Goetz et al. JCO 2017; 35:3638

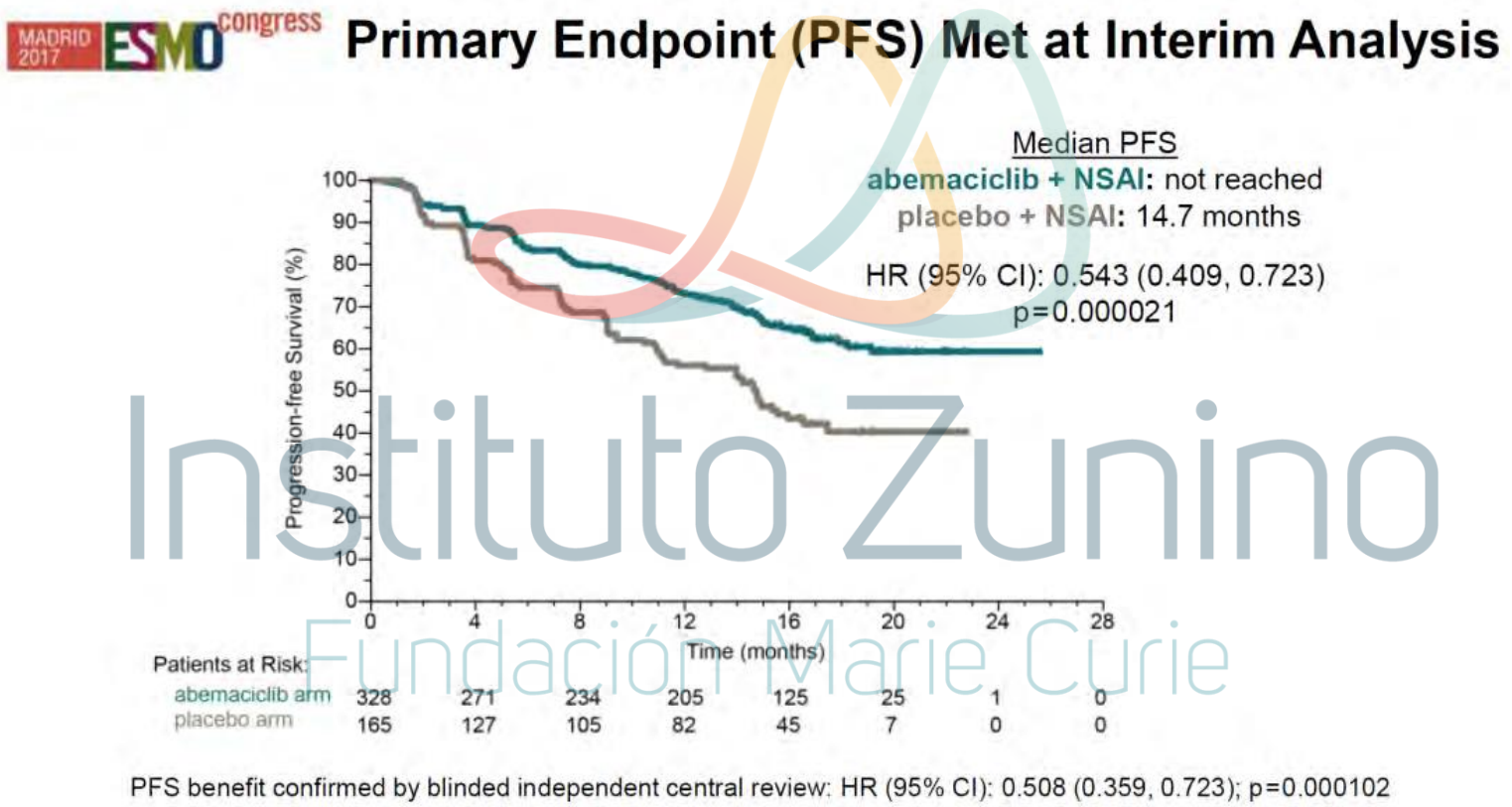
Caracteristicas de los pacientes

		abemaciclib + NSAI n = 328	placebo + NSAI n = 165
Median age (range)		63 (38 – 87)	63 (32 – 88)
Race	Caucasian	186 (56.7)	102 (61.8)
	Asian	103 (31.4)	45 (27.3)
	Other	11 (3.4)	7 (4.2)
Measurable disease	Yes	267 (81.4)	130 (78.8)
	No	61 (18.6)	35 (21.2)
Disease setting	Locoregional recurrent	11 (3.4)	5 (3.0)
	Metastatic recurrent	182 (55.5)	99 (60.0)
	De novo metastatic	135 (41.2)	61 (37.0)
Metastatic site	Visceral	172 (52.4)	89 (53.9)
	Bone-only	70 (21.3)	39 (23.6)
	Other	86 (26.2)	37 (22.4)
Prior neoadjuvant or adjuvant chemotherapy	Yes	125 (38.1)	66 (40.0)
	No	203 (61.9)	99 (60.0)
Prior neoadjuvant or adjuvant endocrine therapy	No endocrine therapy	178 (54.3)	85 (51.5)
	Aromatase inhibitor therapy	85 (25.9)	50 (30.3)
	Other endocrine therapy	65 (19.8)	30 (18.2)
Treatment free interval[a]	<36 months	42/150 (28.0)	32/80 (40.0)
	≥36 months	94/150 (62.7)	40/80 (50.0)
	Unknown	14/150 (9.3)	8/80 (10.0)

[a]Treatment-free interval calculated only for patients with prior endocrine therapy

Goetz et al. JCO 2017; 35:3638

Eficacia



Goetz et al. JCO 2017; 35:3638

Efectos Secundarios

MADRID 2017 ESMO congress

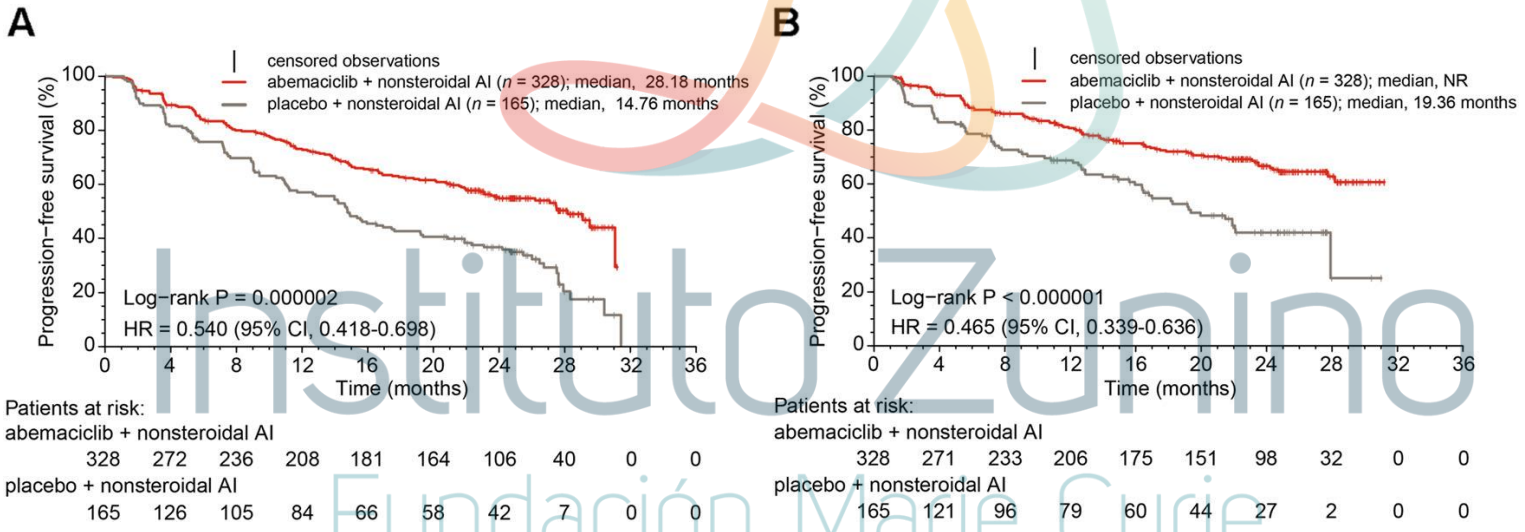
Treatment-emergent Adverse Events (Safety Population) ≥20% Occurrence

	abemaciclib + NSAI n = 327				placebo + NSAI n = 161			
Grade, n (%)	Any	2	3	4	Any	2	3	4
Any adverse event	322 (98.5)	111 (33.9)	159 (48.6)	21 (6.4)	145 (90.1)	61 (37.9)	32 (19.9)	3 (1.9)
Diarrhea	266 (81.3)	89 (27.2)	31 (9.5)	0	48 (29.8)	11 (6.8)	2 (1.2)	0
Neutropenia	135 (41.3)	53 (16.2)	64 (19.6)	5 (1.5)	3 (1.9)	1 (0.6)	1 (0.6)	1 (0.6)
Fatigue	131 (40.1)	55 (16.8)	6 (1.8)	—	51 (31.7)	20 (12.4)	0	—
Nausea	126 (38.5)	36 (11.0)	3 (0.9)	—	32 (19.9)	1 (0.6)	2 (1.2)	—
Abdominal pain	95 (29.1)	21 (6.4)	4 (1.2)	—	19 (11.8)	4 (2.5)	2 (1.2)	—
Anemia	93 (28.4)	45 (13.8)	19 (5.8)	0	8 (5.0)	2 (1.2)	2 (1.2)	0
Vomiting	93 (28.4)	26 (8.0)	4 (1.2)	0	19 (11.8)	3 (1.9)	3 (1.9)	0
Alopecia	87 (26.6)	5 (1.5)	—	—	17 (10.6)	0	—	—
Decreased appetite	80 (24.5)	26 (8.0)	4 (1.2)	0	15 (9.3)	2 (1.2)	1 (0.6)	0
Leukopenia	68 (20.8)	31 (9.5)	24 (7.3)	1 (0.3)	4 (2.5)	1 (0.6)	0	1 (0.6)

- 1 patient experienced non-serious febrile neutropenia in the abemaciclib arm.
- Venous thromboembolic events occurred in 16 (4.9%) of patients in the abemaciclib arm versus 1 (0.6%) in the placebo arm.

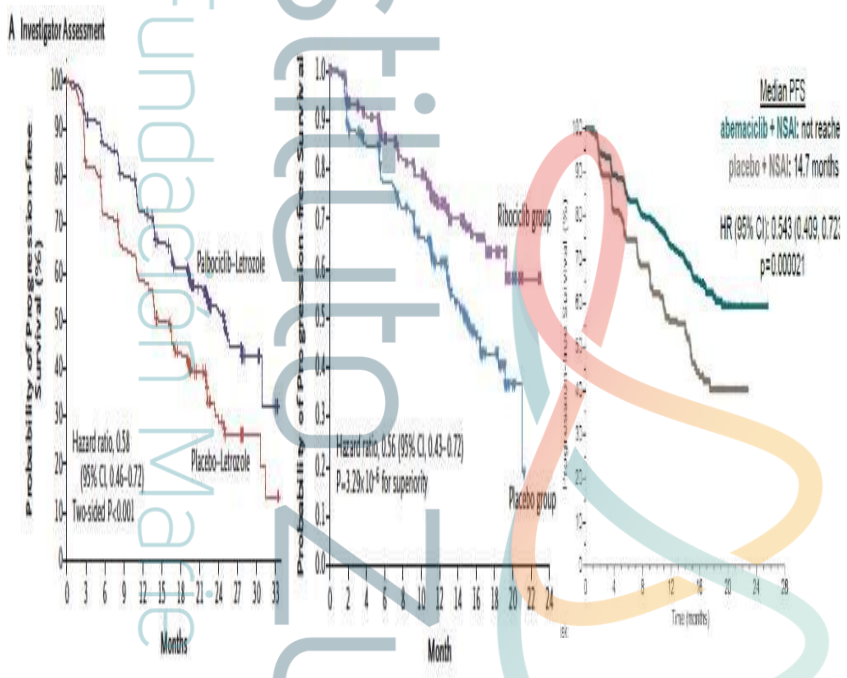
Goetz et al. JCO 2017; 35:3638

Monarch 3: actualizacion



Progression-free survival. **a** Investigator-assessed and **b** Independent central review in the intent-to-treat population. NR, not reached

Johnston et al. NPJ Breast Cancer; published online january 2019

	PALOMA 2 Palbociclib	MONALEESA 2 Ribociclib	MONARCH 3 Abemaciclib
			
PFS	24,8 vs 14,5 m p<0,001	25,3 vs 16 m p<0,001	NR vs 14,7 p<0,001
HR	0.58	0.57	0.54

MONALEESA-7

CLEE011E2301/MONALEESA-7: A Phase III randomized, double-blind, placebo-controlled study of ribociclib with goserelin and tamoxifen or NSAI (letrozole or anastrozole) in premenopausal women with HR+/HER2– advanced breast cancer

Premenopausal women with HR+/HER2– advanced breast cancer

No prior hormonal therapy for advanced disease

N≈660

→

Randomization (1:1)

Stratified by:
- Presence of liver and/or lung metastases
- Prior chemotherapy for advanced disease
- Endocrine combination partner (tamoxifen or NSAI)

→

Ribociclib + goserelin + tamoxifen or NSAI (letrozole or anastrozole)* (n≈330)

Placebo + goserelin + tamoxifen or NSAI (letrozole or anastrozole)* (n≈330)

Primary endpoint
- PFS per RECIST v1.1

Key secondary endpoint
- OS

Other secondary endpoints
- ORR
- CBR
- Time to response
- Duration of response
- ECOG PS
- Safety
- QoL

Exploratory endpoints
- Pharmacokinetics

MONALEESA-7 is the only randomized phase III trial of a CDK4/6 inhibitor focused on premenopausal patients

- *28-day dosing cycles. Once-daily oral doses of tamoxifen (20 mg) or letrozole (2.5 mg) or anastrozole (1 mg) given on Days 1–28 of each cycle. Subcutaneous goserelin implant (3.6 mg) administered on Day 1 of each cycle. Once-daily dose of oral ribociclib (600 mg) or placebo administered on Days 1–21 of each cycle.

Tripathy et al. Lancet Oncol 2018;19: 904

Monaleesa-7: caracteristicas de pacientes

	Ribociclib group (n=335)	Placebo group (n=337)
Age, years	43 (25–58)	45 (29–58)
Race		
White	187 (56%)	201 (60%)
Asian	99 (30%)	99 (29%)
Black	10 (3%)	9 (3%)
Other or unknown	39 (12%)	28 (8%)
ECOG performance status		
0	245 (73%)	255 (76%)
1	87 (26%)	78 (23%)
2	0	1 (<1%)
Missing	3 (1%)	3 (1%)
Disease status at study entry		
Locally advanced	1 (<1%)	1 (<1%)
Metastatic	334 (100%)	336 (100%)
Hormone receptor status		
Oestrogen receptor positive	331 (99%)	335 (99%)
Progesterone receptor positive	290 (87%)	288 (85%)
Disease-free interval*		
Newly diagnosed disease	136 (41%)	134 (40%)
Existing disease	199 (59%)	203 (60%)
≤12 months	23 (7%)	13 (4%)
>12 months	176 (53%)	190 (56%)
Previous neoadjuvant or adjuvant endocrine therapy		
No	208 (62%)	196 (58%)
Yes	127 (38%)	141 (42%)
Progression ≤12 months after endocrine therapy	100 (30%)	105 (31%)
Progression >12 months after endocrine therapy	25 (7%)	35 (10%)
Data missing	2 (1%)	1 (<1%)

(Table 1 continues in next column)

	Ribociclib group (n=335)	Placebo group (n=337)
(Continued from previous column)		
Previous chemotherapy		
For advanced disease	47 (14%)	47 (14%)
Neoadjuvant or adjuvant only	138 (41%)	138 (41%)
None	150 (45%)	152 (45%)
Previous surgery (non-biopsy)		
Yes	202 (60%)	194 (58%)
No	133 (40%)	143 (42%)
Previous radiotherapy		
Yes	161 (48%)	183 (54%)
No	174 (52%)	154 (46%)
Metastatic sites		
0†	1 (<1%)	0
1	112 (33%)	117 (35%)
2	106 (32%)	99 (29%)
≥3	116 (35%)	121 (36%)
Site of metastases		
Soft tissue	25 (7%)	21 (6%)
Bone	251 (75%)	247 (73%)
Bone only	81 (24%)	78 (23%)
Visceral‡	193 (58%)	188 (56%)
Lymph nodes	142 (42%)	158 (47%)
Skin	8 (2%)	8 (2%)

Data are median (range) or number (%). Some percentages do not add up to 100 because of rounding. ECOG=Eastern Cooperative Oncology Group. *Newly diagnosed disease included patients with no first recurrence or progression, or first recurrence or progression within 90 days of diagnosis with no previous anticancer medication. For patients with existing disease, disease-free interval was the time from initial diagnosis to first recurrence or progression. †Patients with locoregionally recurrent (non-metastatic) disease were also eligible. ‡Liver, lung, and any other metastatic site except for soft tissue, bone, skin, and lymph nodes.

Table 1: **Demographics and baseline characteristics**

Tripathy et al. Lancet Oncol 2018;19: 904

Monaleesa-7: eficacia

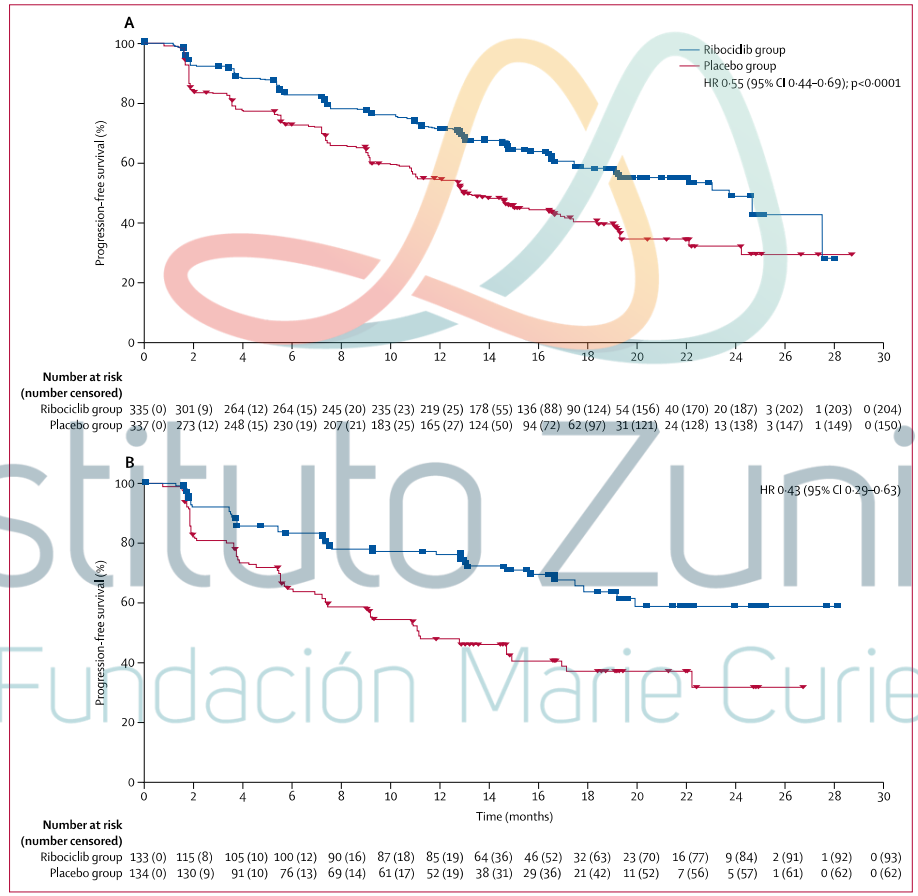


***Figure 2*: Kaplan-Meier analyses of progression-free survival**
Progression-free survival (A) as assessed by the investigators (primary analysis) and (B) as assessed by means of masked, independent central review. HR=hazard ratio.

Tripathy et al. Lancet Oncol 2018;19: 904

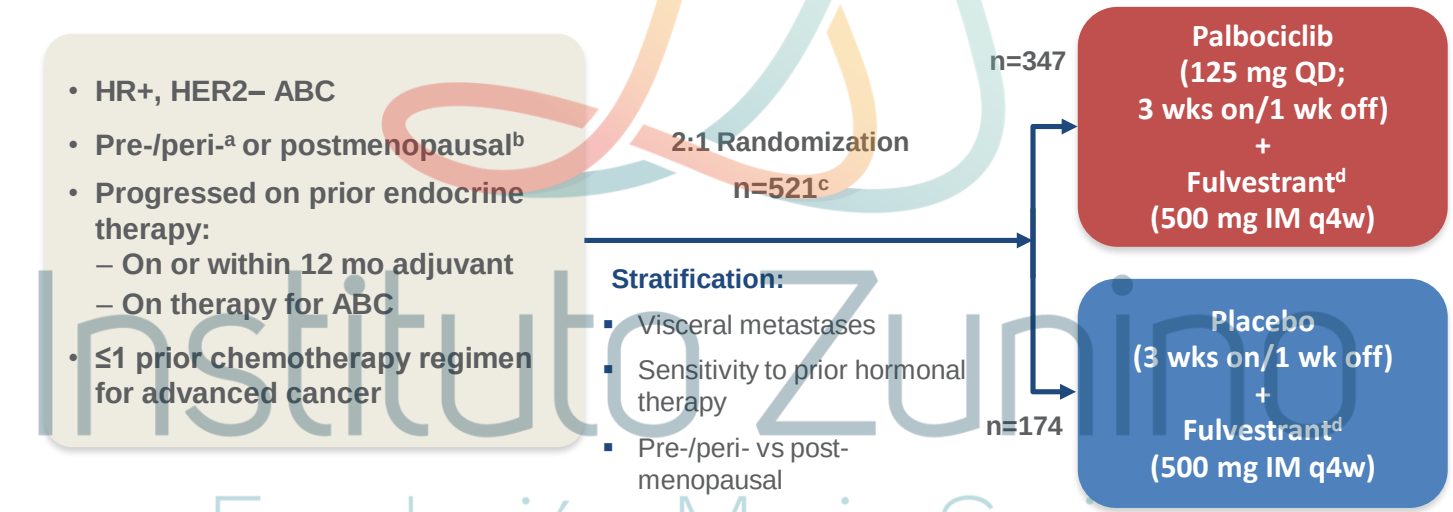
- 2° Linea

Instituto Zunino

Fundación Marie Curie

PALOMA-3

Phase 3, double-blind study involving 144 centers in 17 countries (NCT01942135)



[a]All received goserelin.
[b]Must have progressed on prior endocrine therapy (pre-/perimenopausal) or aromatase inhibitor therapy (postmenopausal).
[c]Patients randomized.
[d]Administered on Days 1 and 15 of Cycle 1, then every 28 d.

Turner NC, et al. N Engl J Med 2015;373:209-219.
Turner NC, et al. ASCO 2015 (Abstract LBA502.

PALOMA-3: caracteristicas de los pacientes

Demographics and Baseline Tumor Characteristics

Characteristic	Palbociclib + Fulvestrant (n=347)	Placebo + Fulvestrant (n=174)
Median age (range), years	57 (30–88)	56 (29–80)
Receptor status, %		
ER+ PR+	69	64
ER+ PR–	26	28
ECOG performance status, %		
0	60	66
1	40	34
Menopausal status,[a] %		
Pre-/peri	21	21
Post	79	79
Visceral metastases,[b] %	59	60
Number of disease sites, %		
1	32	35
2	29	29
≥3	39	36

[a]Based on randomization; [b]lung, liver, brain, pleural, and peritoneal involvement.

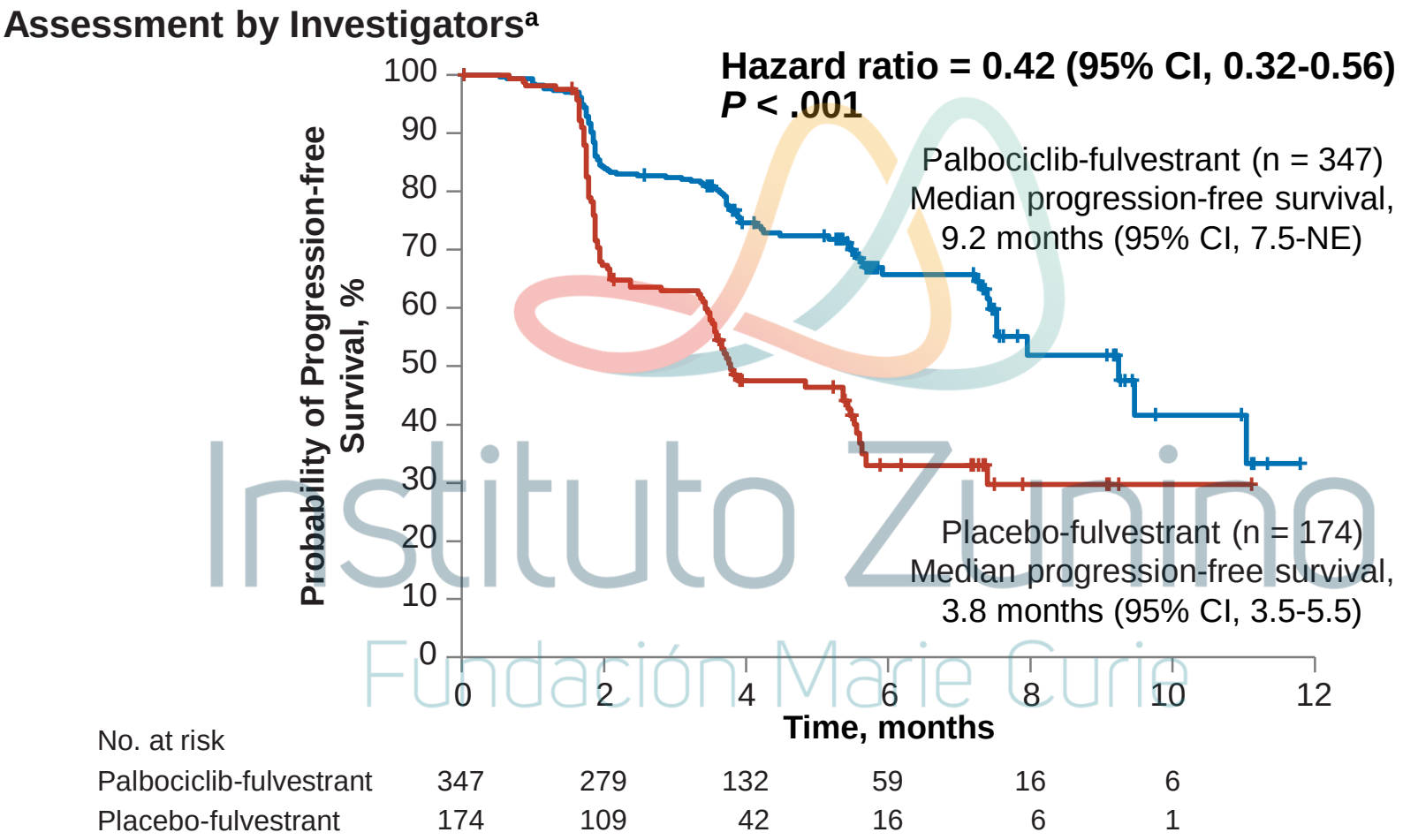
PALOMA-3: caracteristicas de los pacientes (cont)

Tumor Characteristics and Prior Treatment

Characteristic	Palbociclib + Fulvestrant (n=347)	Placebo + Fulvestrant (n=174)
Documented sensitivity to prior hormonal therapy,[a] %		
Yes	79	78
No	21	22
Prior aromatase inhibitor +/- GnRH,[b] %	85	87
Prior tamoxifen +/- GnRH,[b] %	61	60
Prior chemotherapy in advanced setting, %	31	36
Prior lines of therapy in advanced setting, %		
0	24	26
1	38	40
2	26	25
≥3	12	9

[a]Relapsed after 24 months of adjuvant endocrine therapy or had clinical benefit to prior therapy in the advanced setting.
[b]Any prior endocrine therapy anytime before study entry.
GnRH=gonatotropin-releasing hormone.

PALOMA-3: Progression-Free Survival by Investigator Assessment in the Overall Population



CI, confidence interval; NE, not estimable.

[a] Results of a blinded, independent audit were consistent with investigator assessment.

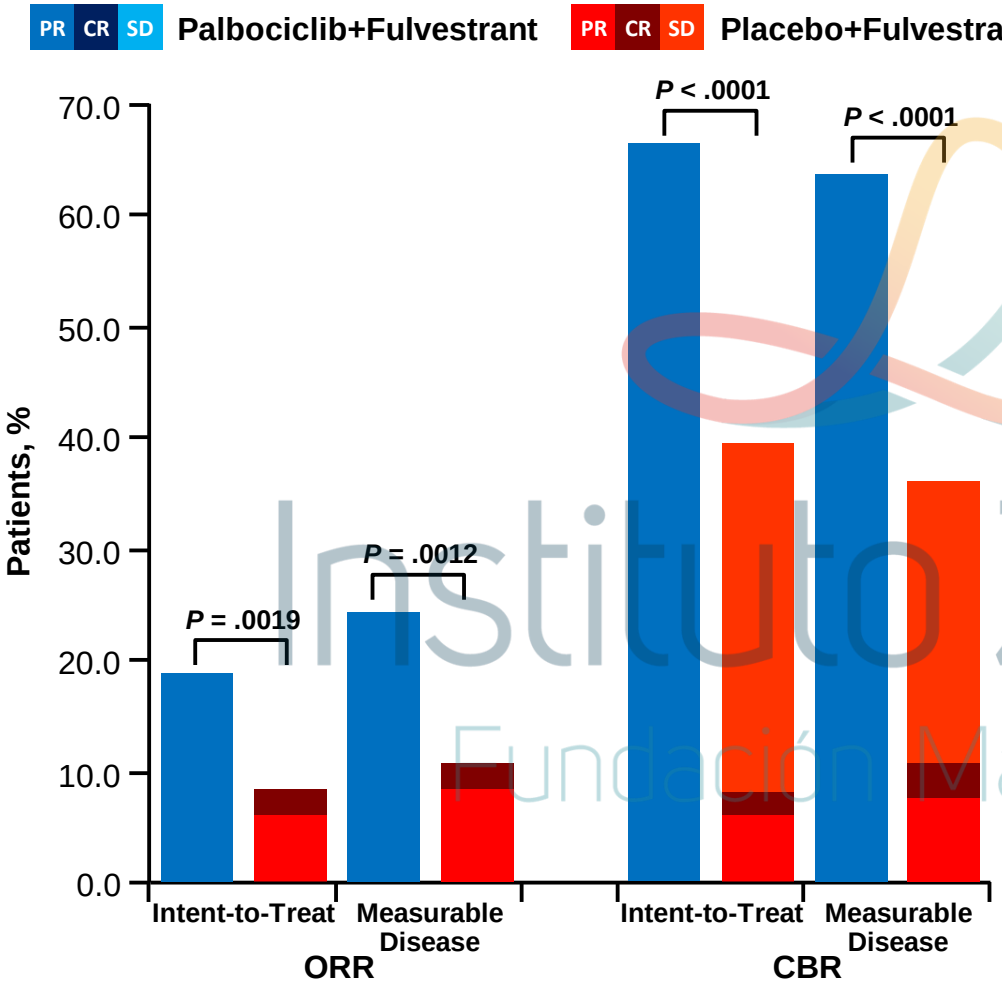
PALOMA-3: Efectos Secundarios

Most Common All-Cause Adverse Events (≥ 20% any grade), n (%)	Palbociclib + Fulvestrant (n = 345)			Placebo + Fulvestrant (n = 172)		
	Any Grade	G3	G4	Any Grade	G3	G4
Neutropenia	272 (79)	184 (53)	30 (9)	6 (3)	0	1 (<1)
Leukopenia	157 (46)	85 (25)	2 (<1)	7 (4)	0	1 (<1)
Fatigue	131 (38)	7 (2)	0	46 (27)	2 (1)	0
Nausea	100 (29)	0	0	45 (26)	1 (<1)	0
Anemia	90 (26)	9 (3)	0	17 (10)	3 (2)	0
Headache	73 (21)	1 (<1)	0	30 (17)	0	0

G, grade.

Data from Turner NC, et al. *N Engl J Med*. 2015;373(3):209-219.

PALOMA-3: actualizacion



Efficacy Measure	PAL+FUL	PBO+FUL
Median PFS, mo	9.5	4.6
	HR = 0.45; 95% CI, 0.36-0.59; *P* < .0001	
CBR, %	66.6	39.7
	P < .0001	
ORR, %	19.0	8.6
	P = .0019	

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; FUL, fulvestrant; HR, hazard ratio; PBO, placebo; PR, partial response; ORR, objective response rate; PAL, palbociclib; PFS, progression free survival; SD, stable disease.

Cristofanilli et al Lancet Oncol 2016; 17:425

PALOMA-3: Confirmed Efficacy in Endocrine-Sensitive /-Refractory Disease

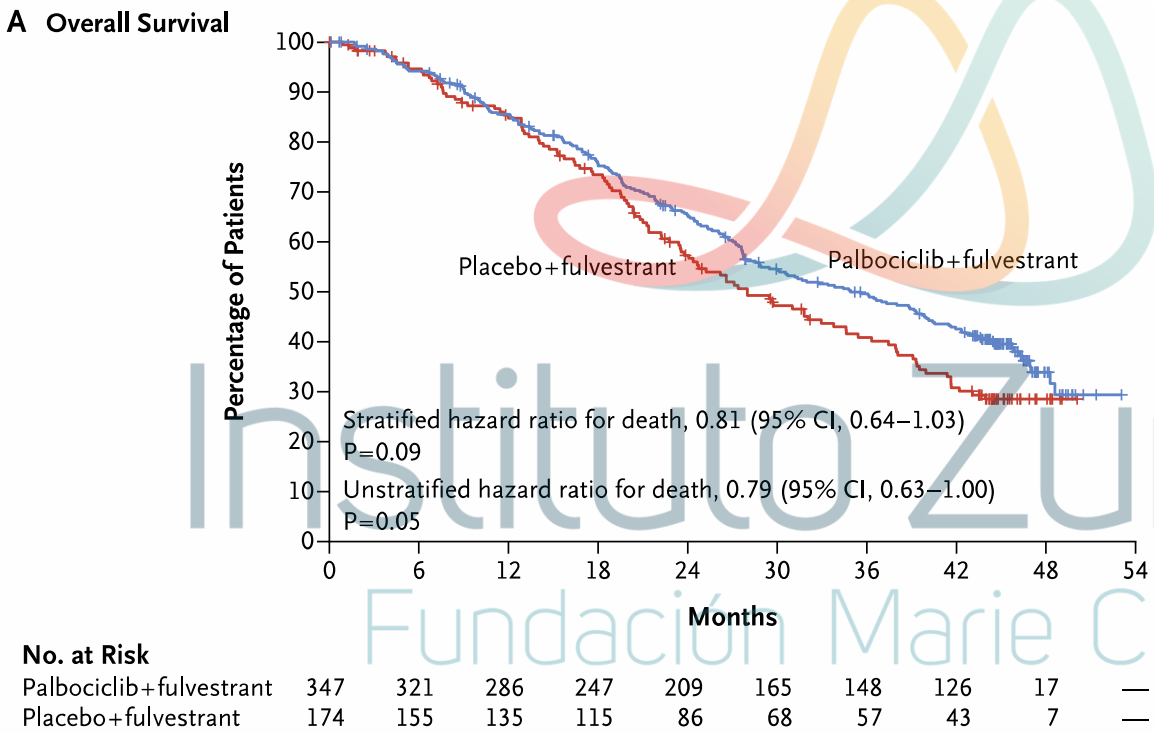
- PFS benefit with PAL+FUL was maintained across predefined subgroups

Patient Subgroup PFS[1]	PAL+FUL, mo	PBO+FUL, mo	HR (95% CI) *P* value
Pre/perimenopausal	9.5 (n = NR)	5.6 (n = NR)	0.50 (0.29-0.87) *P* = .0065
No prior systemic therapy	9.5 (n = 74)	5.4 (n = 40)	0.55 (0.32-0.92) *P* = .0214
Responsive to prior ET	10.2 (n = 274)	4.2 (n = 136)	0.42 (0.32-0.56) *P* < .0001
AI as most recent therapy	9.5 (n = 217)	3.7 (n = 119)	0.42 (0.31-0.56) *P* < .0001

AI, aromatase inhibitor; CI, confidence interval; ET, endocrine therapy; FUL, fulvestrant; NR, not reported; PAL, palbociclib; PFS, progression-free survival.

Cristofanilli et al Lancet Oncol 2016; 17:425

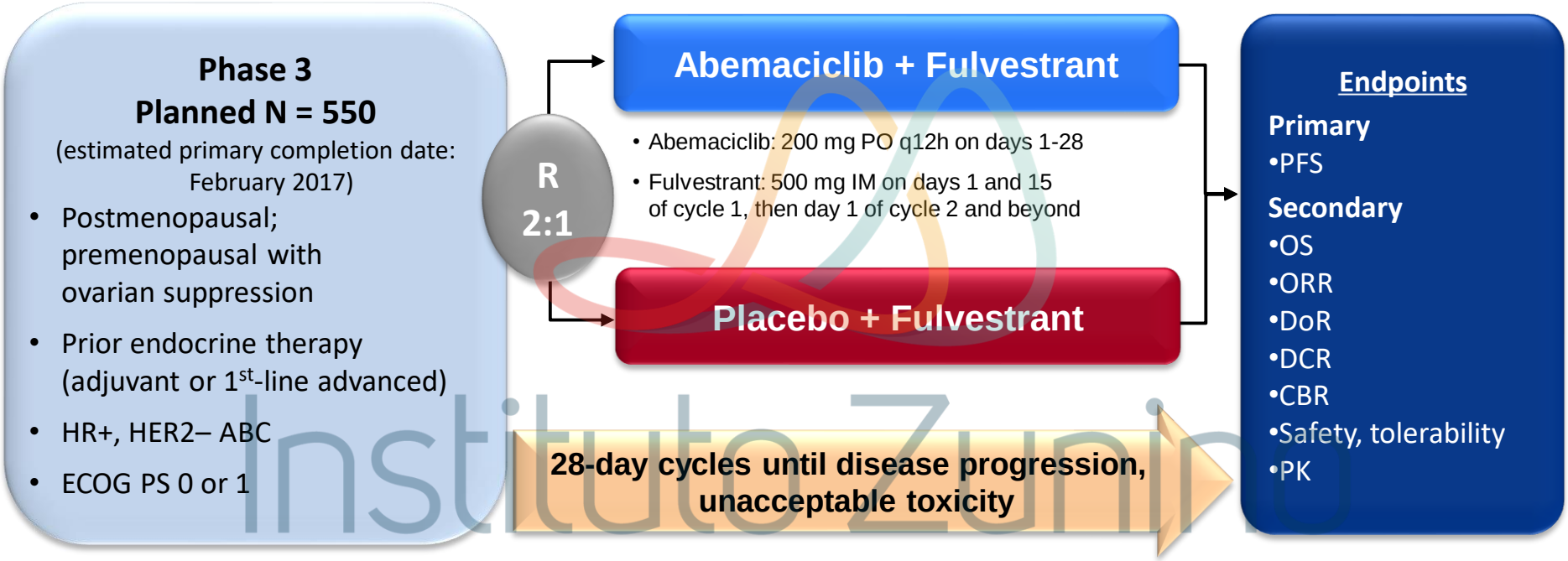
Paloma-3: OS



	No. of Patients	Median Overall Survival (95% CI)
		mo
Palbociclib+ Fulvestrant	347	34.9 (28.8–40.0)
Placebo+ Fulvestrant	174	28.0 (23.6–34.6)

Turner et al. NEJM 2018; 379:1926

MONARCH-2



Stratified for visceral vs bone mets or others, sensitivity to endocrine therapy

ABC, advanced breast cancer; CBR, clinical benefit rate; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2–, human epidermal growth factor receptor-2–negative; HR+, hormone receptor-positive; IM, intramuscularly; mets, metastases; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PO, orally; q12h, every 12 hours; R, randomization.

Sledge et al. JCO 2017; 35:2875

Monarch-2: caracteristicas de pacientes

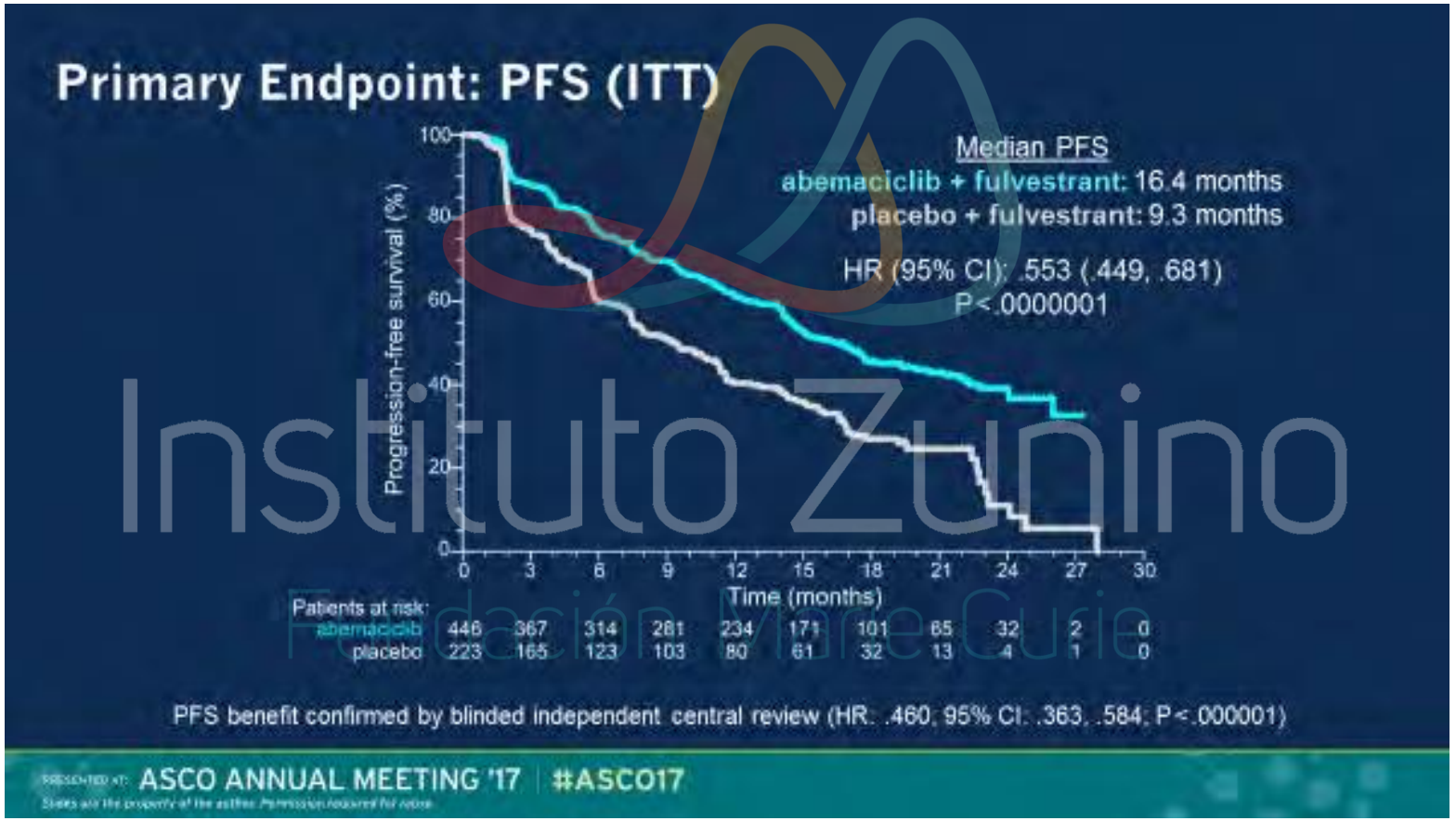
Table 1. Patient and Disease Baseline Characteristics

Characteristic	Abemaciclib + Fulvestrant (n = 446)	Placebo + Fulvestrant (n = 223)
Age, years, median (range)	59 (32-91)	62 (32-87)
ET resistance*		
Primary	111 (24.9)	58 (26.0)
Secondary	326 (73.1)	163 (73.1)
Most recent ET†		
Neoadjuvant or adjuvant	263 (59.0)	133 (59.6)
Metastatic	171 (38.3)	85 (38.1)
Prior AI		
Yes	316 (70.9)	149 (66.8)
No	130 (29.1)	74 (33.2)
PgR status‡		
Positive	339 (76.0)	171 (76.7)
Negative	96 (21.5)	44 (19.7)
Metastatic site§		
Visceral	245 (54.9)	128 (57.4)
Bone only	123 (27.6)	57 (25.6)
Other	75 (16.8)	38 (17.0)
Measurable disease		
Yes	318 (71.3)	164 (73.5)
No	128 (28.7)	59 (26.5)
Race‖		
Asian	149 (33.4)	65 (29.1)
Caucasian	237 (53.1)	136 (61.0)
Other	29 (6.5)	13 (5.8)
ECOG performance status¶		
0	264 (59.2)	136 (61.0)
1	176 (39.5)	87 (39.0)
Prior chemotherapy for neoadjuvant or adjuvant treatment		
Yes	267 (59.9)	134 (60.1)
No	179 (40.1)	89 (39.9)
Menopausal status#		
Pre- or perimenopause	72 (16.1)	42 (18.8)
Postmenopause	371 (83.2)	180 (80.7)

Note. Data given as No. (%) unless otherwise indicated.
Abbreviations: AI, aromatase inhibitor; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; PgR, progesterone receptor.
*Six patients in the abemaciclib arm and two patients in the placebo arm had not received prior ETs.
†ET history was not available for 12 patients in the abemaciclib arm and five patients in the placebo arm.
‡Eight patients in each arm had unknown PgR status.
§Metastatic site was not available for three patients in the abemaciclib arm.
‖A total of 31 patients in the abemaciclib arm and nine in the placebo arm had missing race information.
¶One patient had ECOG performance status of 2 in the abemaciclib arm.
#Menopausal status was not available for three patients in the abemaciclib arm and one in the placebo arm.

Sledge et al. JCO 2017; 35:2875

Monarch-2: eficacia



Sledge et al. JCO 2017; 35:2875

Monarch-2: analisis de subgrupos

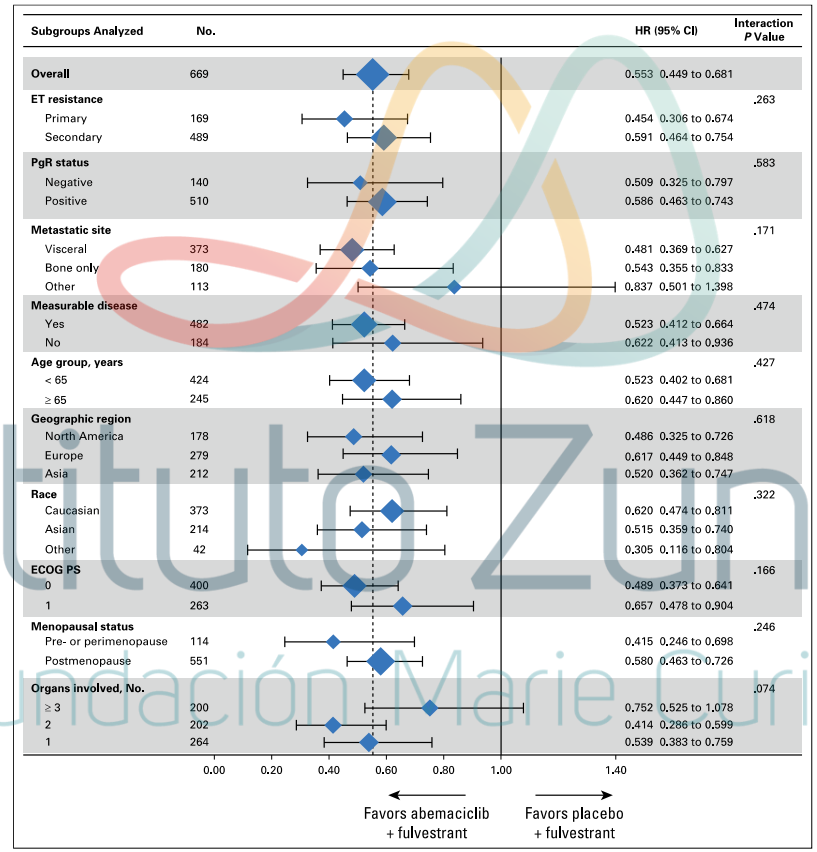


Fig 3. Progression-free survival (PFS) of patient subgroups. HRs are for abemaciclib versus placebo. *P* values are for the interaction term from a model with arm, the subgroup variable and arm × subgroup interaction term. PFS HRs are indicated by diamonds and 95% CIs are indicated by the crossing horizontal lines. Diamond size is proportional to each patient subgroup population size. HRs are unstratified and estimated with the adjustment of arm × subgroup interaction, except the overall PFS. The overall PFS estimates were stratified by metastatic site and ET resistance. The factor levels that consisted of < 5% of randomly assigned patients were omitted from the analysis. ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; PgR, progesterone receptor.

Sledge et al. JCO 2017; 35:2875

Quien se beneficia? Quien no?

Instituto Zunino

Fundación Marie Curie

Quien se beneficia? Quien no?

- Biomarcadores

Biomarcadores

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29: 640–645, 2018
doi:10.1093/annonc/mdx784
Published online 11 December 2017

ORIGINAL ARTICLE

Polyclonal *RB1* mutations and acquired resistance to CDK 4/6 inhibitors in patients with metastatic breast cancer

R. Condorelli[1†], L. Spring[2†], J. O'Shaughnessy[3,4], L. Lacroix[1], C. Bailleux[1], V. Scott[1], J. Dubois[2], R. J. Nagy[5], R. B. Lanman[5], A. J. Iafrate[2], F. Andre[1†] & A. Bardia[2*,†]

CONCLUSIONES

- Sécuenciacion ctDNA antes de empezar el tratamiento con anti-CDK 4/6 y a la progresion
- Tres pacientes
- Fueron identificadas mutaciones adquiridas de *RB1* a los 5, 8 y 13 meses (no presentes antes del tratamiento)
- Presion sobre el blanco? (como ESR1-IAs)
- Asociacion a otras terapias blanco (Inhibidores de PI3K)?

Condorelli et al . Annals of Oncology 29: 640–645, 2018 Published online 11 December 2017

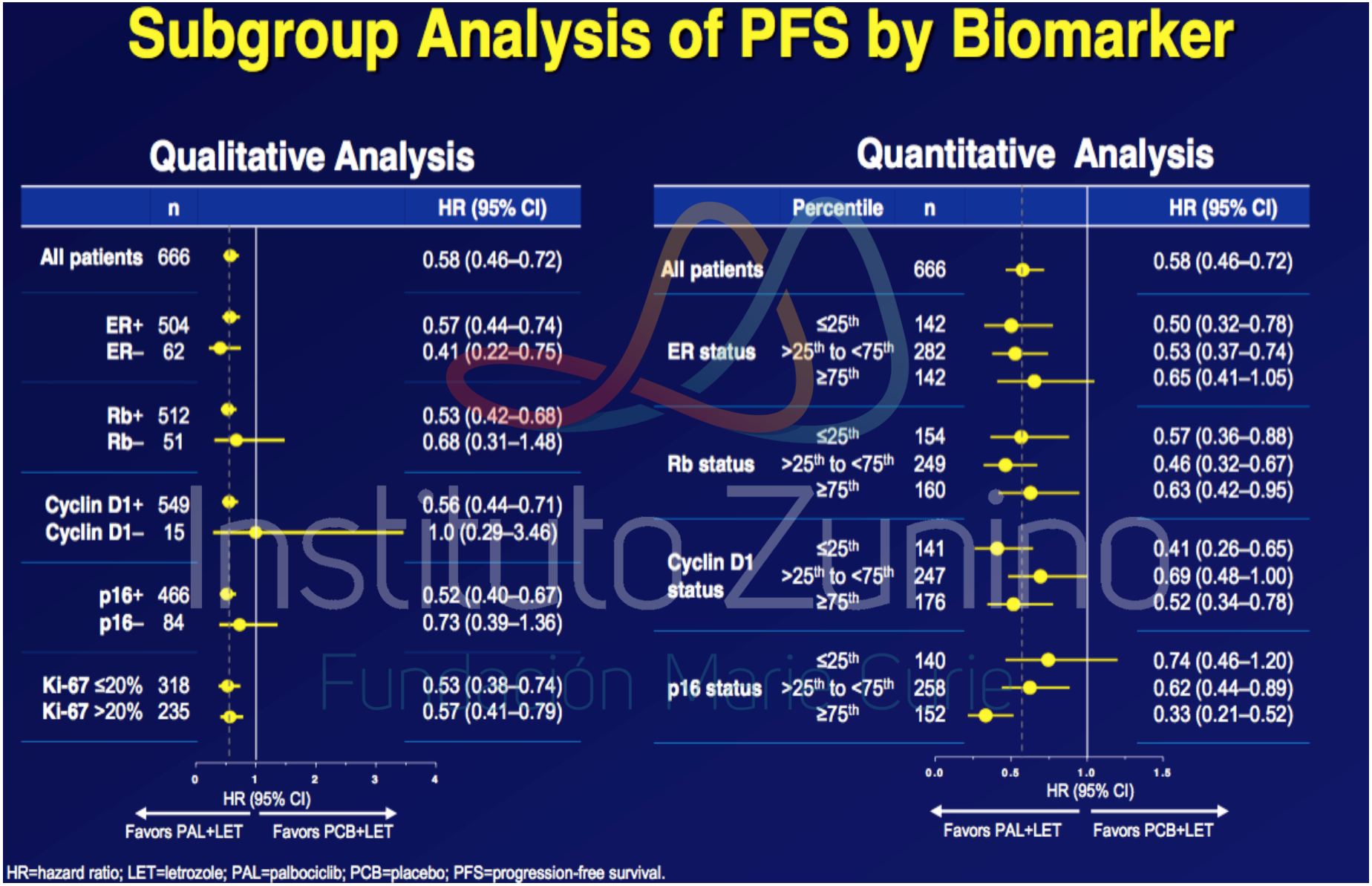
COPENHAGEN 2016 ESMO congress

BIOMARKER ANALYSES FROM THE PHASE 3 PALOMA-2 TRIAL OF PALBOCICLIB WITH LETROZOLE COMPARED WITH PLACEBO PLUS LETROZOLE IN POSTMENOPAUSAL WOMEN WITH ER+/HER2– ADVANCED BREAST CANCER

Richard S. Finn[1], Yuqui Jiang[2], Hope S. Rugo[3], Stacy Moulder[4], Seock-Ah Im[5], Karen Gelmon[6], Veronique Dieras[7], Miguel Martin[8], Anil Abraham Joy[9], Masakazu Toi[10], Eric Gauthier[2], Dongrui R. Lu[2], Cynthia Huang Bartlett[11], Dennis J. Slamon[1]

[1]David Geffen School of Medicine, Los Angeles, CA, USA; [2]Pfizer Inc, La Jolla, CA, USA; [3]University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [4]University of Texas, MD Anderson Cancer Center, Houston, TX, USA; [5]Seoul National University Hospital, Seoul, Korea; [6]British Columbia Cancer Agency, Vancouver, BC, Canada; [7]Institut Curie, Paris, France; [8]Hospital Gregorio Maranon, Universidad Complutense, Madrid, Spain; [9]Cross Cancer Institute, University of Alberta, Edmonton, Alberta, Canada; [10]Kyoto University Hospital, Kyoto, Japan; [11]Pfizer Inc, New York, NY, USA

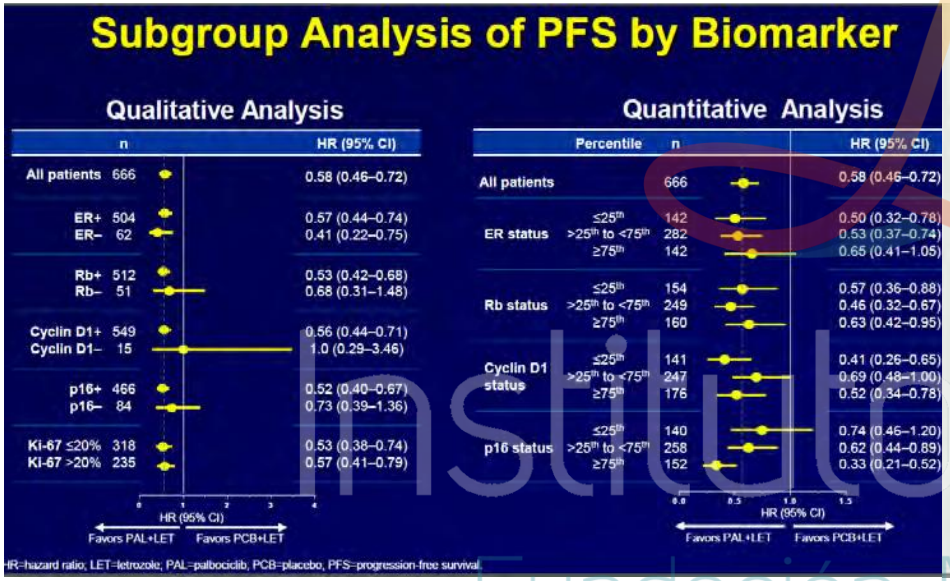
Subgroup Analysis of PFS by Biomarker

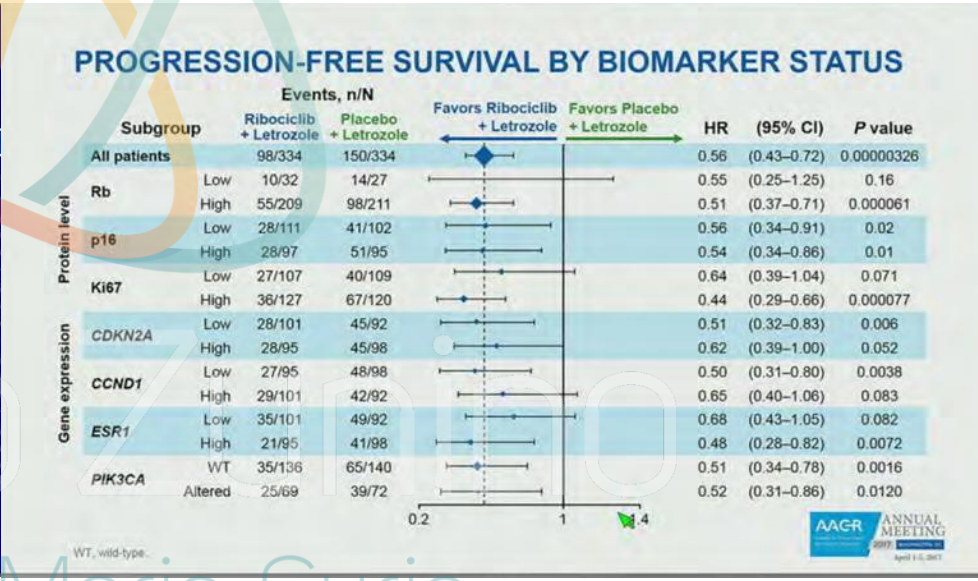


HR=hazard ratio; LET=letrozole; PAL=palbociclib; PCB=placebo; PFS=progression-free survival.

Turner et al. Annals of Oncology 29: 669–680, 2018 Published online 11 January 2018

Biomarcadores





Paloma[2]

Monaleesa[2]

Quien se beneficia? Quien no?

- Biomarcadores

- Evolucion clinica

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29: 669–680, 2018
doi:10.1093/annonc/mdx797
Published online 11 January 2018

ORIGINAL ARTICLE

Clinical considerations of the role of palbociclib in the management of advanced breast cancer patients with and without visceral metastases

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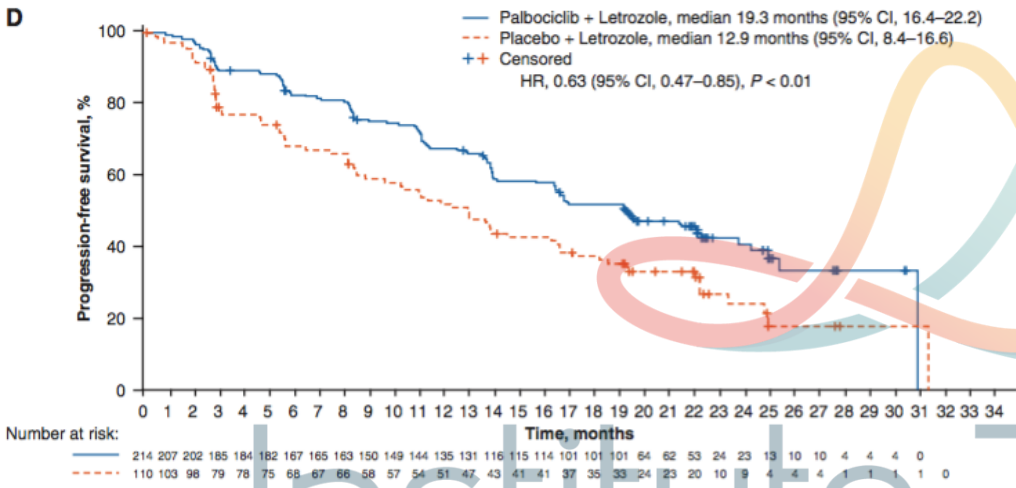
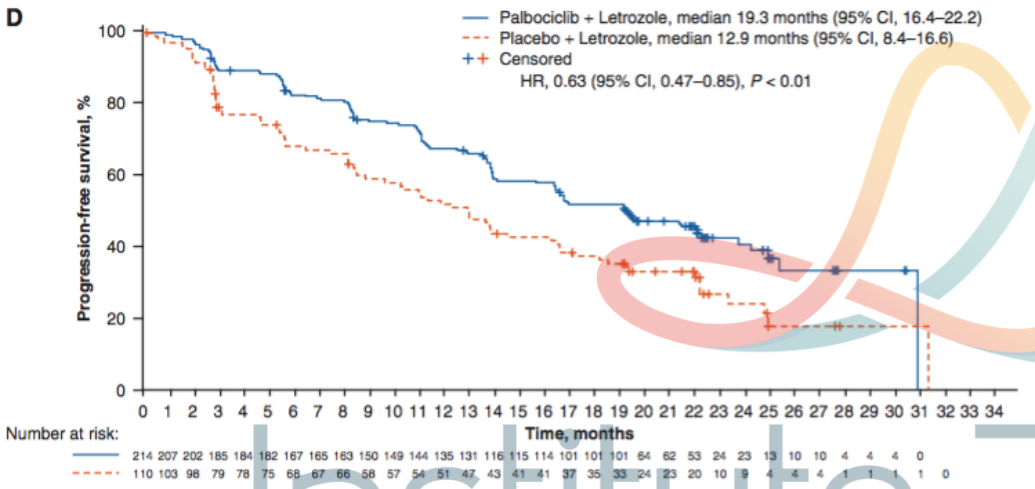
Table 1. Demographic and baseline characteristics by treatment group for patients with and without visceral metastases

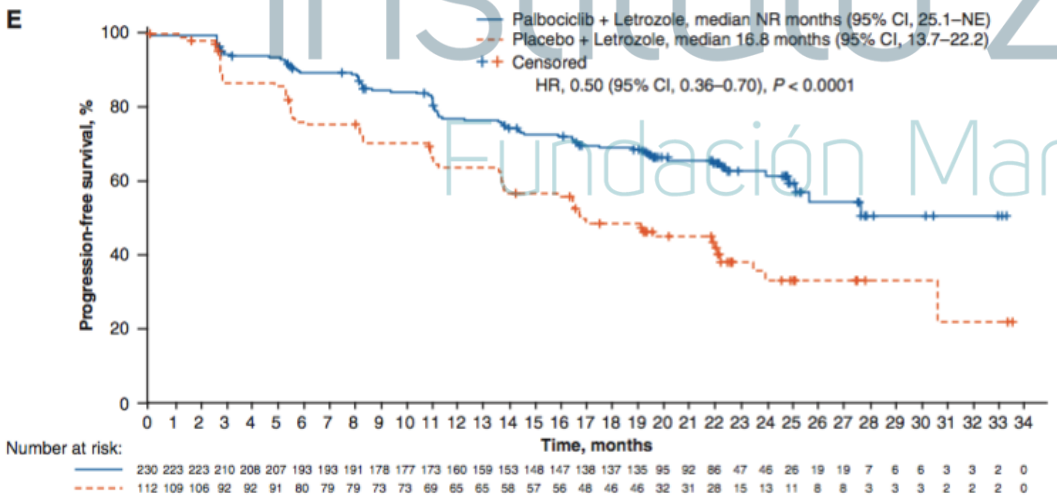
Characteristics	PALOMA-3[a,b]				PALOMA-2[a,b]			
	PAL + FUL		PBO + FUL		PAL + LET		PBO + LET	
	Visceral (*n* = 200)	Nonvisceral (*n* = 147)	Visceral (*n* = 104)	Nonvisceral (*n* = 70)	Visceral (*n* = 214)	Nonvisceral (*n* = 230)	Visceral (*n* = 110)	Nonvisceral (*n* = 112)
Median (range) age, years	57.0 (30.0–88.0)	57.0 (33.0–82.0)	58.5 (35.0–80.0)	54.0 (29.0–74.0)	62.0 (30.0–88.0)	62.0 (36.0–89.0)	61.0 (28.0–88.0)	62.0 (32.0–88.0)
Involved disease sites[c]								
Liver	125 (62.5)	–	80 (76.9)	–	75 (35.0)	–	46 (41.8)	–
Lymph node	97 (48.5)	41 (27.9)	39 (37.5)	24 (34.3)	125 (58.4)	87 (37.8)	65 (59.1)	45 (40.2)
Bone	136 (68.0)	128 (87.1)	76 (73.1)	54 (77.1)	126 (58.9)	199 (86.5)	73 (66.4)	89 (79.5)
Peritoneum	1 (<1)	–	0	–	4 (1.9)	–	0	–
Number of metastatic organ sites[c]								
1	17 (8.5)	94 (63.9)	11 (10.6)	49 (70.0)	17 (7.9)	121 (52.6)	6 (5.5)	60 (53.6)
2	63 (31.5)	32 (21.8)	37 (35.6)	14 (20.0)	63 (29.4)	54 (23.5)	26 (23.6)	26 (23.2)
3	58 (29.0)	15 (10.2)	27 (26.0)	6 (8.6)	66 (30.8)	46 (20.0)	41 (37.3)	20 (17.9)
4	43 (21.5)	3 (2.0)	20 (19.2)	0	45 (21.0)	7 (3.0)	23 (20.9)	6 (5.4)
>4	18 (9.0)	2 (1.4)	9 (8.7)	0	23 (10.7)	2 (<1.0)	14 (12.7)	0
ECOG performance status								
0	114 (57.0)	92 (62.6)	66 (63.5)	50 (71.4)	113 (52.8)	144 (62.6)	51 (46.4)	51 (45.5)
1	86 (43.0)	55 (37.4)	38 (36.5)	20 (28.6)	97 (45.3)	81 (35.2)	59 (53.6)	58 (51.8)
2	–	–	–	–	4 (1.9)	5 (2.2)	0	3 (2.7)
Prior endocrine therapy[d]								
Tamoxifen only	4 (2.0)	1 (<1.0)	3 (2.9)	1 (1.4)	72 (33.6)	59 (25.7)	40 (36.4)	33 (29.5)
Aromatase inhibitor	23 (11.5)	21 (14.3)	9 (8.7)	7 (10.0)	14 (6.5)	19 (8.3)	8 (7.3)	20 (17.9)
Both tamoxifen and aromatase inhibitor	96 (48.0)	63 (42.9)	50 (48.1)	31 (44.3)	38 (17.8)	40 (17.4)	15 (13.6)	10 (8.9)

PALOMA 2 (1° linea)

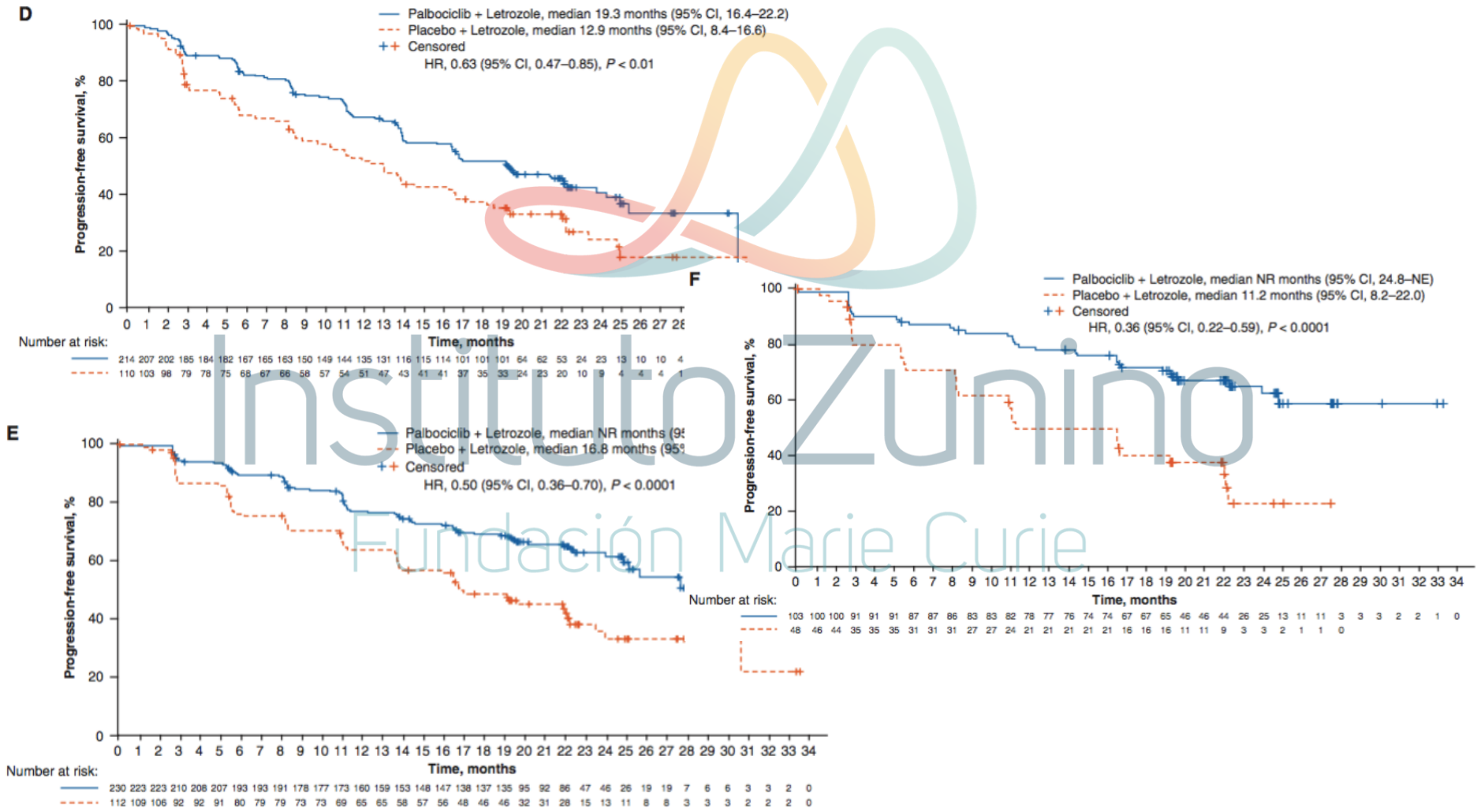


PALOMA 2 (1° linea)

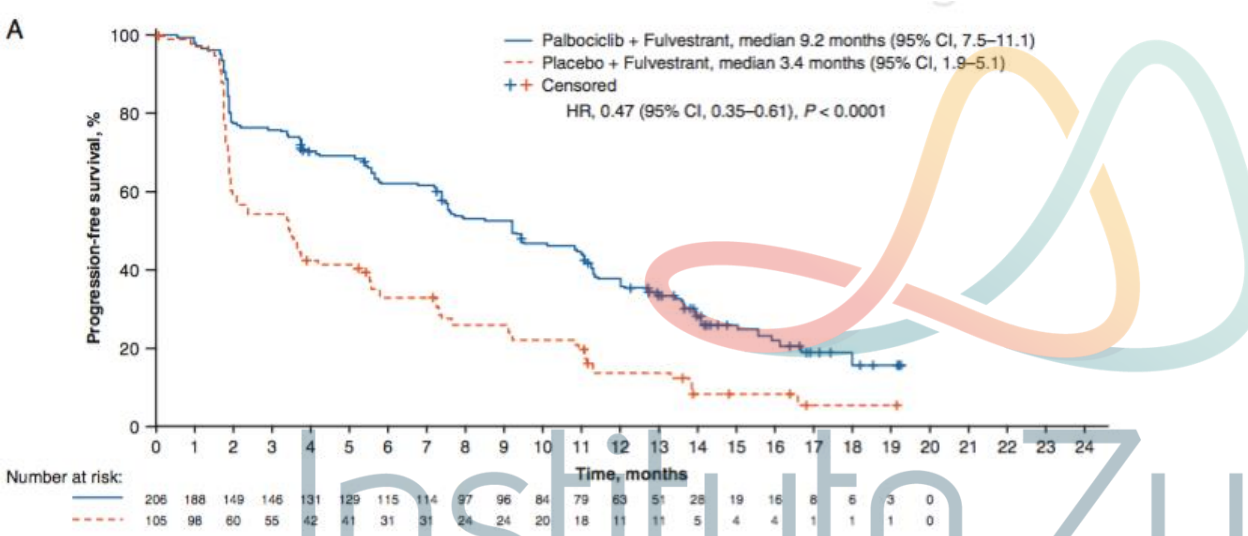




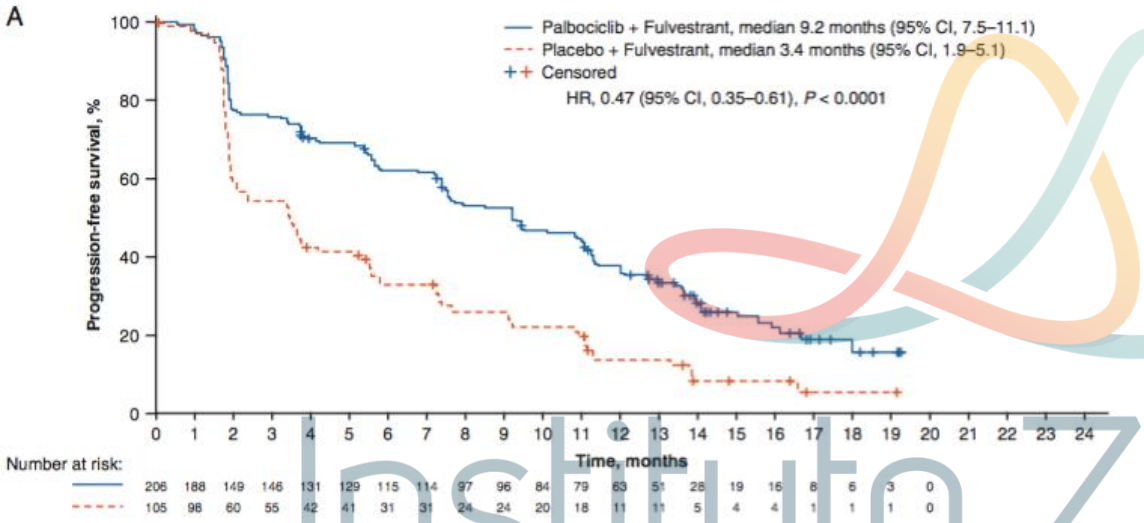
PALOMA 2 (1° linea)

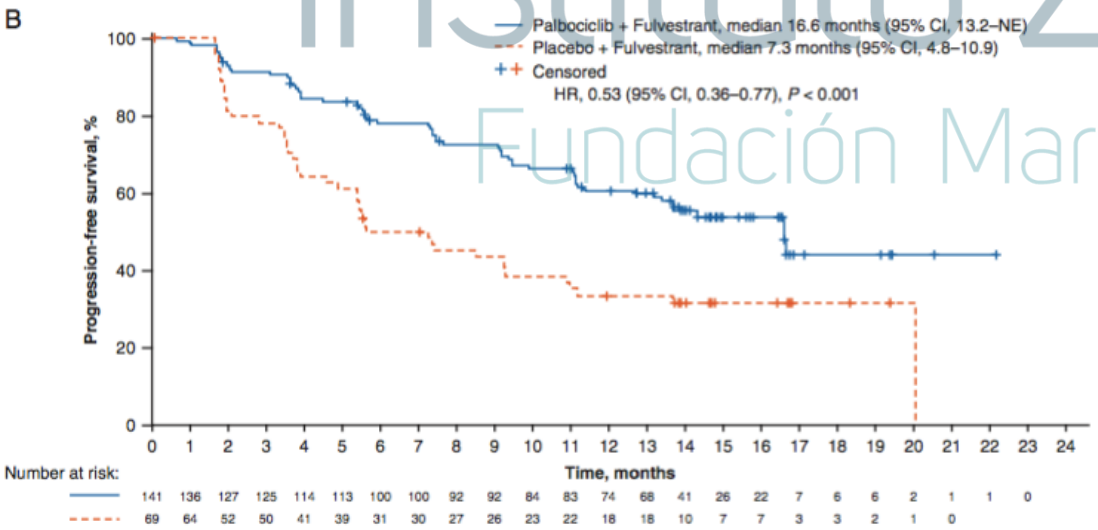


PALOMA 3 (2° linea)

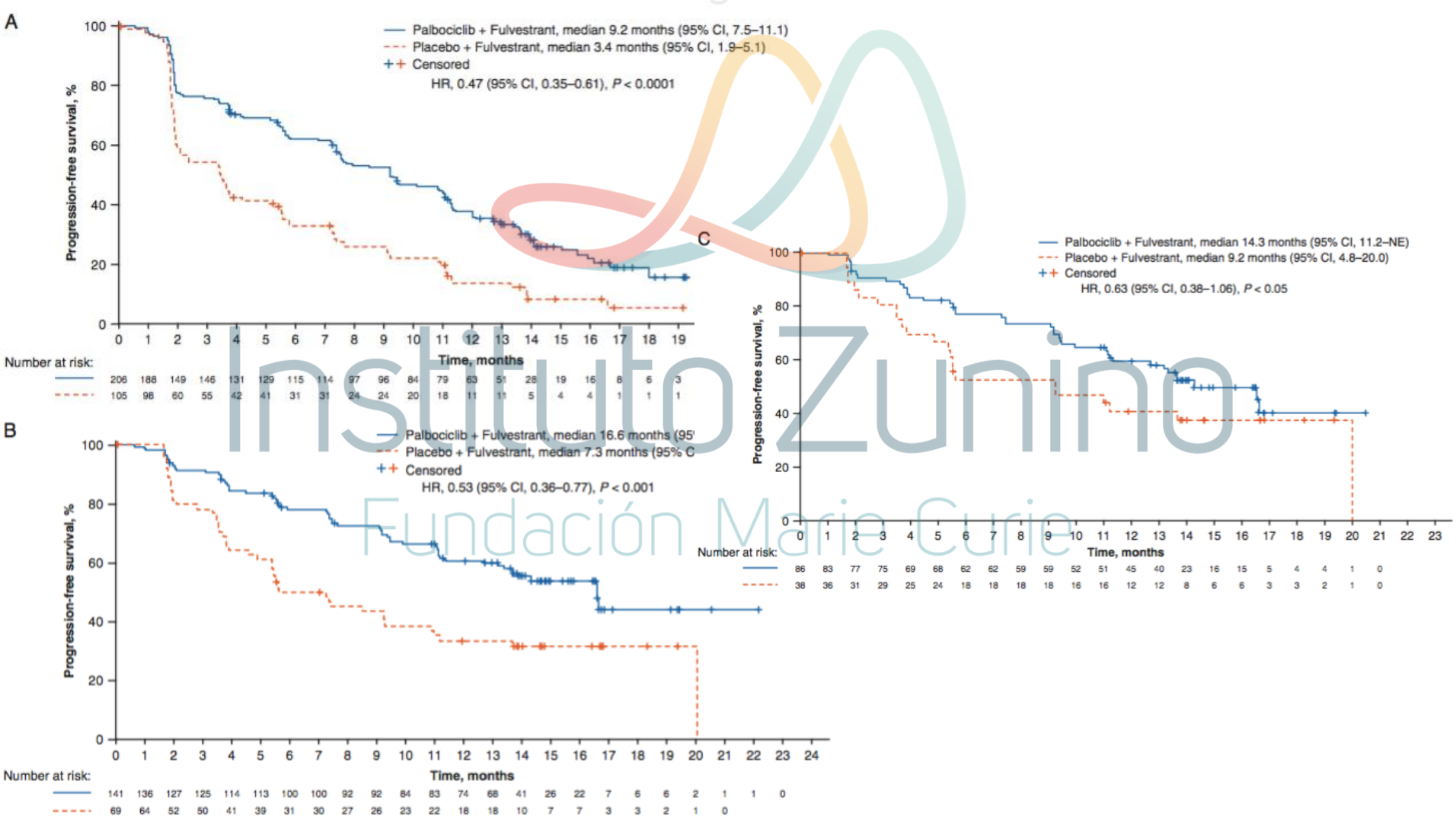


PALOMA 3 (2° linea)





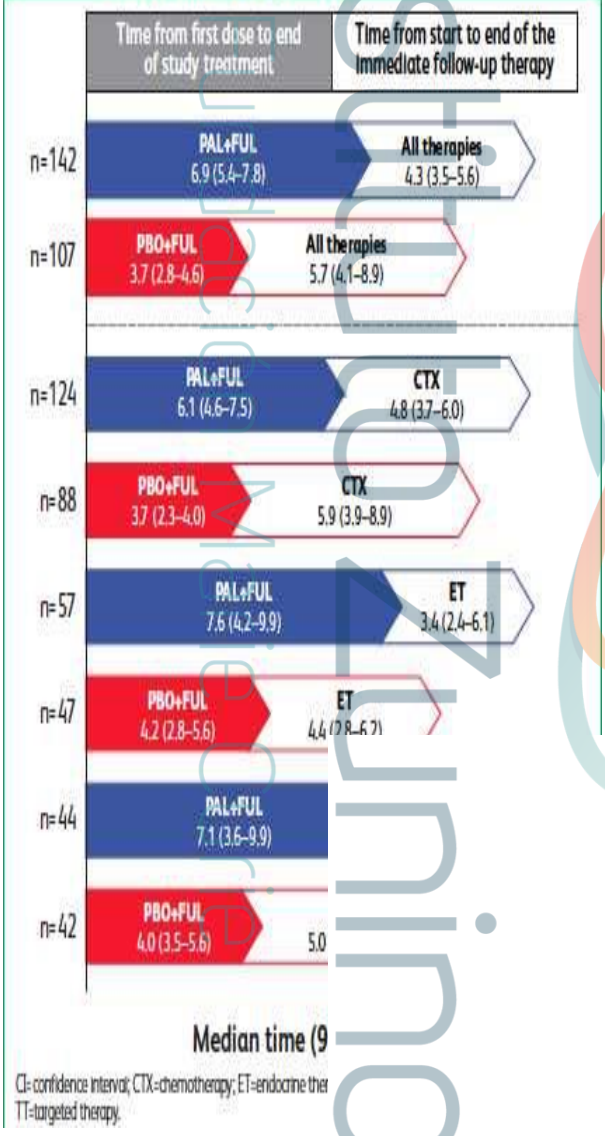
PALOMA 3 (2° linea)



Y despues de CDKi?

2016 SAN ANTONIO BREAST CANCER SYMPOSIUM
DEC. 6-10 Henry B. Gonzalez Convention Center, San Antonio, Texas, USA

Figure 5. Kaplan-Meier Estimates of Treatment Durations For Patients on Poststudy Therapy for Disease Progression (PALOMA 3)



Après échappement sous Palbociclib, pas de perte d'efficacité de la ligne de traitement ultérieure

...albociclib
...t line of
... treatment
... has no effect on the therapeutic benefit derived from subsequent treatments.

Conclusiones

- Nuevo estandar de tratamiento en la enfermedad RH+ HER2- metastasica

Guias internacionales

ASCO GUIDELINES

- NCCN and ABC guidelines indicates that ET is recommended as first line treatment even in the presence of visceral disease
- Current guidelines recommend the use of CT only in the presence of life threatening disease or visceral crisis

1. NCCN Guidelines Breast Cancer, version 2.2016
2. Rugo HS *et al. J Clin Oncol* 2016
3. Cardoso F *et al. Annals Oncol* 2017

HRs de estudios

MADRID 2017 ESMO congress

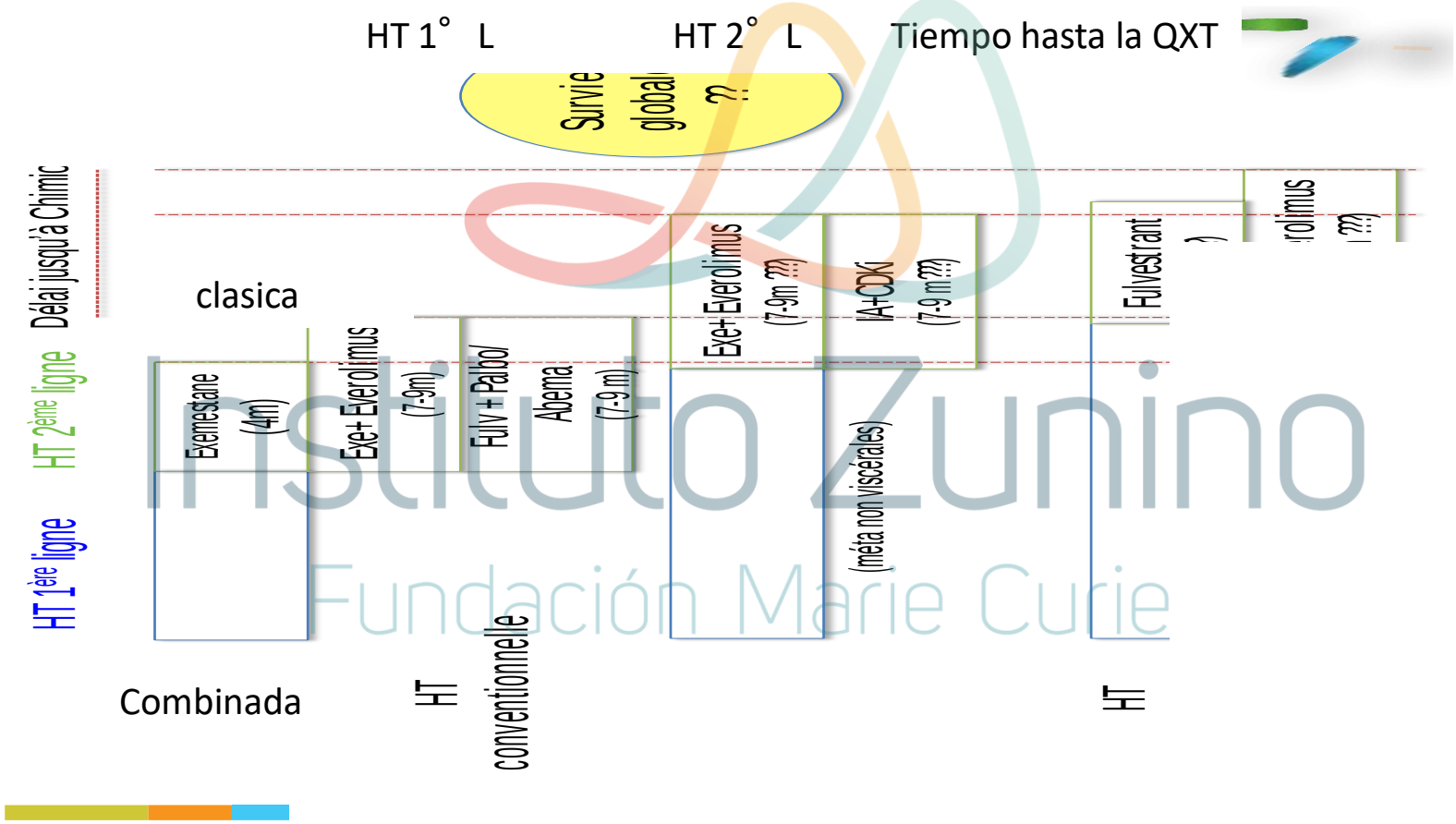
Registration trials of CDK4/6 inhibitors

First line AI sensitive – with AI		HR	(95% CI)
PALOMA2	Palbociclib	**0.58**	(0.46, 0.72)
MONALEESA2	Ribociclib	**0.58**	(0.46, 0.70)
MONARCH3	Abemaciclib	**0.54**	(0.41, 0.72)
Endocrine pre-treated – with fulvestrant			
PALOMA3	Palbociclib	**0.50**	(0.40, 0.62)
MONARCH2	Abemaciclib	**0.55**	(0.45, 0.68)

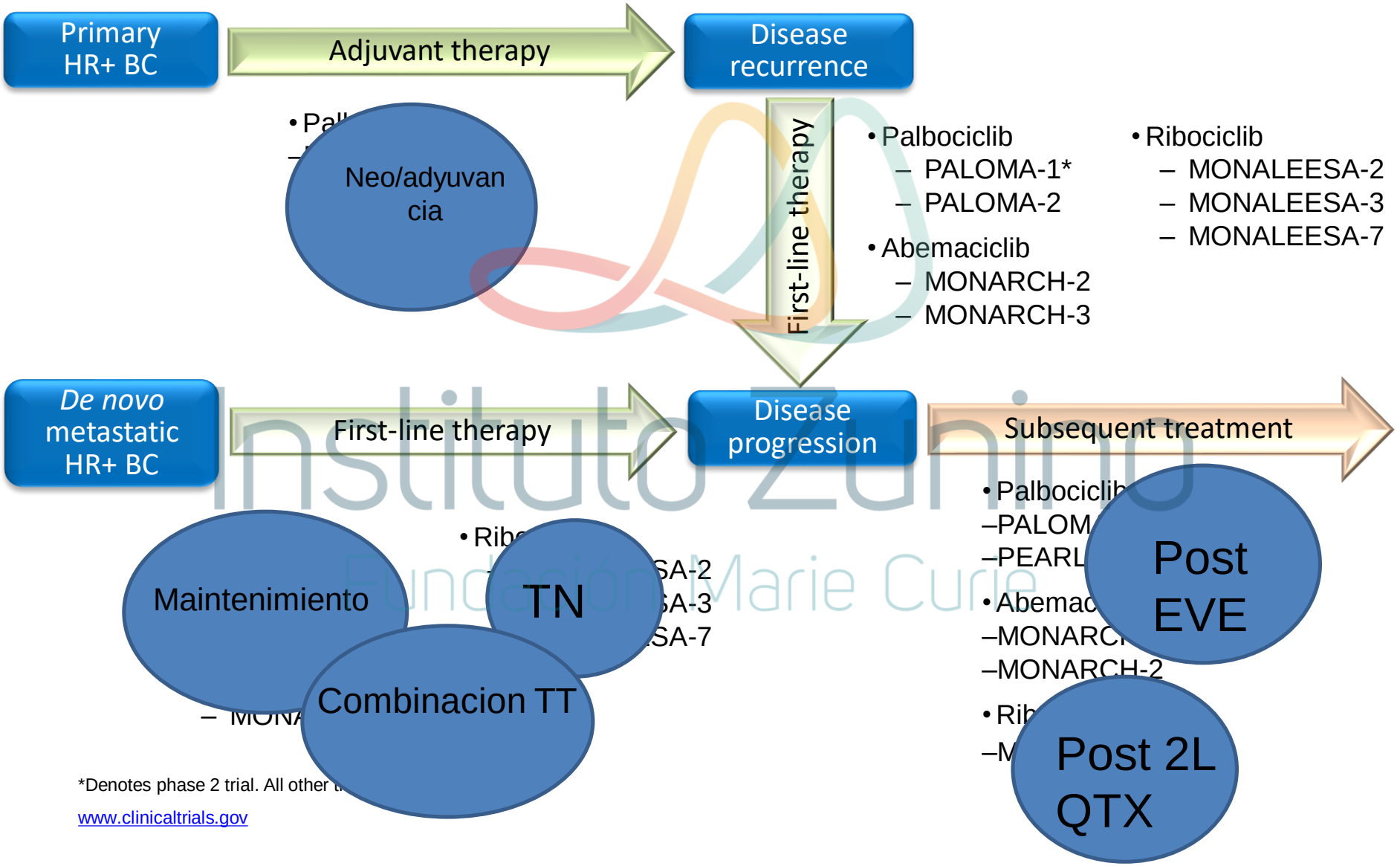
Hazard ratios for PFS primary endpoint

Finn RS, *et al.* NEJM 2016, Turner NC, *et al.* NEJM 2015
updated SABCS 2016, Hortobagyi GN, et al. NEJM 2016
updated ASCO 2017, Sledge, *et al* JCO 2017

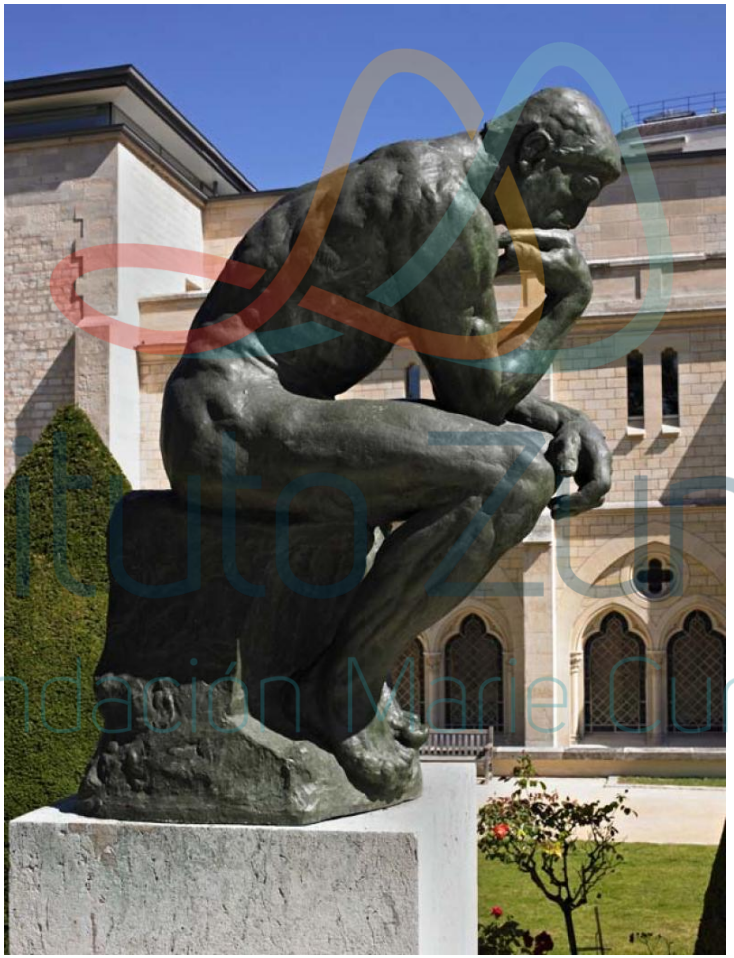
Cuando?



Overview of Key Trials With CKD inhibitors in HR+, HER2– Breast Cancer



Cual elegir??



- Estado hormonal (menopausia o no)
- Administracion
- Perfil de tolerancia (neutropenia +/- alargamiento QT +/- diarrea)
- Biomarcadores? Non…
- Sobrevida Global???

FRANCHE-COMTÉ
IRFC
INSTITUT RÉGIONAL FÉDÉRATIF DU CANCER

CHRU Besançon
centre hospitalier régional universitaire

Muchas gracias