TRIALs of CDK4/6 inhibitor in women with hormone-receptor-positive metastatic breast cancer

Marta Bonotto

Department of Oncology
University Hospital of Udine

TRIALs of CDK4/6 inhibitor in women with hormone-receptor-positive metastatic breast cancer

ABOUT METHODOLOGY

Marta Bonotto

Department of Oncology
University Hospital of Udine

- OPPORTUNITIES
- OBJECTIVES
- DESIGN
- ENDPOINTS
- POPULATION
- RESULTS
- CONSIDERATIONS

- **OPPORTUNITIES**
- OBJECTIVES
- DESIGN
- ENDPOINTS
- POPULATION
- RESULTS
- CONSIDERATIONS

TRIALs of CDK4 and CDK6 inhibitor in women with hormone-receptor-positive metastatic breast cancer

Feasible

Interesting

Novel

Ethical

Relevant

TRIALs of CDK4 and CDK6 inhibitor in women with hormone-receptor-positive metastatic breast cancer

40,000 new cases of MBC per year in the US
The most frequently diagnosed cancer in women
60-65% of cases hormone receptor-positive

Feasible

Interesting

Novel

Ethical

Relevant

TRIALs of CDK4 and CDK6 inhibitor in women with hormone-receptor-positive metastatic breast cancer

40,000 new cases of MBC per year in the US
The most frequently diagnosed cancer in women
60-65% of cases hormone receptor-positive

Palbociclib:
first-in-class,
oral, selective
CDK-4/6 inhibitor

Feasible

Interesting

Novel

Ethical

Relevant

TRIALs of CDK4 and CDK6 inhibitor in women with hormone-receptor-positive metastatic breast cancer

40,000 new cases of MBC per year in the US
The most frequently diagnosed cancer in women
60-65% of cases hormone receptor-positive

Feasible

Palbociclib:
first-in-class,
oral, selective
CDK-4/6 inhibitor

Interesting

Overexpression of CDK-4/6 associated with proliferation of ER+ and/or PgR+ breast cancer

Novel

Ethical

Relevant

TRIALs of CDK4 and CDK6 inhibitor in women with hormone-receptor-positive metastatic breast cancer

40,000 new cases of MBC per year in the US
The most frequently diagnosed cancer in women
60-65% of cases hormone receptor-positive

Feasible

Palbociclib:
first-in-class,
oral, selective
CDK-4/6 inhibitor

Interesting

Overexpression of CDK-4/6 associated with proliferation of ER+ and/or PgR+ breast cancer

Novel

Ethical

Endocrine therapy as
the mainstain of treatment in this setting

Relevant

De-novo resistance
Acquired resistance

- OPPORTUNITIES
- **OBJECTIVES**
- DESIGN
- ENDPOINTS
- POPULATION
- RESULTS
- CONSIDERATIONS

BOLERO-2

≥2° line
Everolimus+exemestane
vs. placebo+exemestane

Primary Purpose: Treatment

ENHANCING THE EFFICACY OF ENDOCRINE THERAPY

BOLERO-2

≥2° line
Everolimus+exemestane
vs. placebo+exemestane

PALOMA -1

1° line
palbociclib+letrozole
vs. letrozole

PALOMA -3

≥2° line
palbociclib+fulvestrant
vs. placebo+fulvestrant

Primary Purpose: Treatment

ENHANCING THE EFFICACY OF ENDOCRINE THERAPY

BOLERO-2

≥2° line
Everolimus+exemestane
vs. placebo+exemestane

Study First Received: March, 2009
Results First Received: July, 2012

PALOMA -1

1° line
palbociclib+letrozole
vs. letrozole

Study First Received: July, 2008
Results First Received: March, 2015

PALOMA -3

≥2° line
palbociclib+fulvestrant
vs. placebo+fulvestrant

Study First Received: September, 2013
Estimated Study Completion Date: January, 2017
Primary Completion Date: December, 2014
(Final data collection date for primary outcome measure)

ClinicalTrials.gov

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer

José Baselga, M.D., Ph.D., Mario Campone, M.D., Ph.D., Martine Piccart, M.D., Ph.D., Howard A. Burris III, M.D., Hope S. Rugo, M.D., Tarek Sahmoud, M.D., Ph.D., Shinzaburo Noguchi, M.D., Michael Gnant, M.D., Kathleen I. Pritchard, M.D., Fabienne Lebrun, M.D., J. Thaddeus Beck, M.D., Yoshinori Ito, M.D., Denise Yardley, M.D., Ines Deleu, M.D., Alejandra Perez, M.D., Thomas Bachelot, M.D., Ph.D., Luc Vittori, M.Sc., Zhiying Xu, Ph.D., Pabak Mukhopadhyay, Ph.D., David Lebwohl, M.D., and Gabriel N. Hortobagyi, M.D.

N ENGL J MED 366;6 NEJM.ORG FEBRUARY 9, 2012

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]

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

The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study

Richard S Finn, John P Crown, Istvan Lang, Katalin Boer, Igor M Bondarenko, Sergey O Kulyk, Johannes Ettl, Ravindranath Patel, Tamas Pinter, Marcus Schmidt, Yaroslav Shparyk, Anu R Thummala, Nataliya L Voytko, Camilla Fowst, Xin Huang, Sindy T Kim, Sophia Randolph, Dennis J Slamo

Lancet Oncol 2015; 16: 25–35

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 16, 2015 VOL. 373 NO. 3

Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer

Nicholas C. Turner, M.D., Ph.D., Jungsil Ro, M.D., Fabrice André, M.D., Ph.D., Sherene Loi, M.D., Ph.D., Sunil Verma, M.D., Hiroji Iwata, M.D., Nadia Harbeck, M.D., Sibylle Loibl, M.D., Cynthia Huang Bartlett, M.D., Ke Zhang, Ph.D., Carla Giorgetti, Ph.D., Sophia Randolph, M.D., Ph.D., Maria Koehler, M.D., Ph.D., and Massimo Cristofanilli, M.D.

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

Massimo Cristofanilli, Nicholas C Turner*, Igor Bondarenko, Jungsil Ro, Seock-Ah Im, Norikazu Masuda, Marco Colleoni, Angela DeMichele, Sherene Loi, Sunil Verma, Hiroji Iwata, Nadia Harbeck, Ke Zhang, Kathy Puyana Theall, Yuqiu Jiang, Cynthia Huang Bartlett, Maria Koehler, Dennis Slamon*

Lancet Oncol 2016; 17: 425–39

- OPPORTUNITIES
- OBJECTIVES
- **DESIGN**
- ENDPOINTS
- POPULATION
- RESULTS
- CONSIDERATIONS

PALOMA -1

1° line
palbociclib+letrozole
vs. letrozole

DESIGN: two part study design: Phase I-II – screening design

PALOMA -3

≥2° line
palbociclib+fulvestrant vs.
placebo+fulvestrant

DESIGN: Phase III

PALOMA -1

1° line
palbociclib+letrozole
vs. letrozole

DESIGN: two part study design: Phase I-II – screening design
INTERVENTION: parallel assignment
ALLOCATION: randomized

PALOMA -3

≥2° line
palbociclib+fulvestrant vs.
placebo+fulvestrant

DESIGN: Phase III
INTERVENTION: parallel assignment
ALLOCATION: randomized

PALOMA -1

1° line
palbociclib+letrozole
vs. letrozole

DESIGN: two part study design: Phase I-II – screening design
INTERVENTION: parallel assignment
ALLOCATION: randomized
OPEN LABEL

PALOMA -3

≥2° line
palbociclib+fulvestrant vs.
placebo+fulvestrant

DESIGN: Phase III
INTERVENTION: parallel assignment
ALLOCATION: randomized
PLACEBO-CONTROLLED: Masking: Double Blind (Subject, Caregiver, Investigator)

PALOMA -1

1° line
palbociclib+letrozole
vs. letrozole

DESIGN: two part study design: Phase I-II – screening design
INTERVENTION: parallel assignment
ALLOCATION: randomized 1:1
OPEN LABEL

PALOMA -3

≥2° line
palbociclib+fulvestrant vs.
placebo+fulvestrant

DESIGN: Phase III
INTERVENTION: parallel assignment
ALLOCATION: randomized 2:1
PLACEBO-CONTROLLED: Masking: Double Blind (Subject, Caregiver, Investigator)

PALOMA -1

1° line
palbociclib+letrozole
vs. letrozole

Main assumption:
114 PFS events to have 80% power to detect a hazard ratio of 0.67
53% increase in median PFS → 9 months vs. 13.5 months
with a one-side significance level of α=0.10

Parameter (estimate)	Results
Primary endpoint: PFS	
Sample size with main assumption: 150 in cohort 2	
Interim analysis for early stopping	
50% of the total PFS events: 57	

PALOMA -1

1° line
palbociclib+letrozole
vs. letrozole

Main assumption:
114 PFS events to have 80% power to detect a hazard ratio of 0.67
53% increase in median PFS → 9 months vs. 13.5 months
with a one-side significance level of α=0.10

Parameter (estimate)	Results
Primary endpoint: PFS	
Sample size with main assumption: 150 in cohort 2	Unplanned interim analysis (31 events in cohort 1)
Interim analysis for early stopping	
50% of the total PFS events: 57	

PALOMA -1

1° line
palbociclib+letrozole
vs. letrozole

Main assumption:
114 PFS events to have 80% power to detect a hazard ratio of 0.67
53% increase in median PFS → 9 months vs. 13.5 months
with a one-side significance level of α=0.10

Parameter (estimate)	Results
Primary endpoint: PFS	
Sample size with main assumption: 150 in cohort 2	Unplanned interim analysis (31 events in coh CCND1 gene amplification Loss of p16
Interim analysis for early stopping	
50% of the total PFS events: 57	

PALOMA -1

1° line
palbociclib+letrozole
vs. letrozole

Main assumption:
114 PFS events to have 80% power to detect a hazard ratio of 0.67
53% increase in median PFS → 9 months vs. 13.5 months
with a one-side significance level of α=0.10

Parameter (estimate)	Results
Primary endpoint: PFS	
Sample size with main assumption: 150 in cohort 2	Unplanned interim analysis (31 events in cohort 1) ↓ 165 in cohort 1 and 2
Interim analysis for early stopping	
50% of the total PFS events: 57	61 ↓ **FALL IN THE EVENT RATE over time**

PALOMA -1

1° line
palbociclib+letrozole
vs. letrozole

Main assumption:
114 PFS events to have 80% power to detect a hazard ratio of 0.67
53% increase in median PFS → 9 months vs. 13.5 months
with a one-side significance level of α=0.10

Parameter (estimate)	Results
Primary endpoint: PFS	
Sample size with main assumption: 150 in cohort 2	Unplanned interim analysis (31 events in cohort 1) ↓ 165 in cohort 1 and 2
Interim analysis for early stopping	
50% of the total PFS events: 57	61

↓

Adjustment:
95 PFS events to have 98% power to detect a hazard ratio of 0.50
75% power to detect a hazard ratio of 0.67
with a one-side significance level of α=0.10

PALOMA -3

≥2° line
palbociclib+fulvestrant vs.
placebo+fulvestrant

Main assumption:
238 PFS events to have 90% power to detect a hazard ratio of 0.64
56% increase in median PFS → 6 months vs. 9.4 months
with a one-side significance level of α=0.025

Parameter (estimate)	Results
Primary endpoint: PFS	
Sample size with main assumption: 417	521
Interim analysis for early stopping	
60% of the total PFS events: 143	195
Pre-specified Haybittle-Peto boundary α=0.00135	P<0.001

- OPPORTUNITIES
- OBJECTIVES
- DESIGN
- **ENDPOINTS**
- POPULATION
- RESULTS
- CONSIDERATIONS

PALOMA -1

1° line
palbociclib+letrozole
vs. letrozole

PRIMARY ENDPOINT: Phase I : overall safety profile of PD 0332991 (time frame: 14 mo)
II : progression free survival (time frame: 3.5 years)

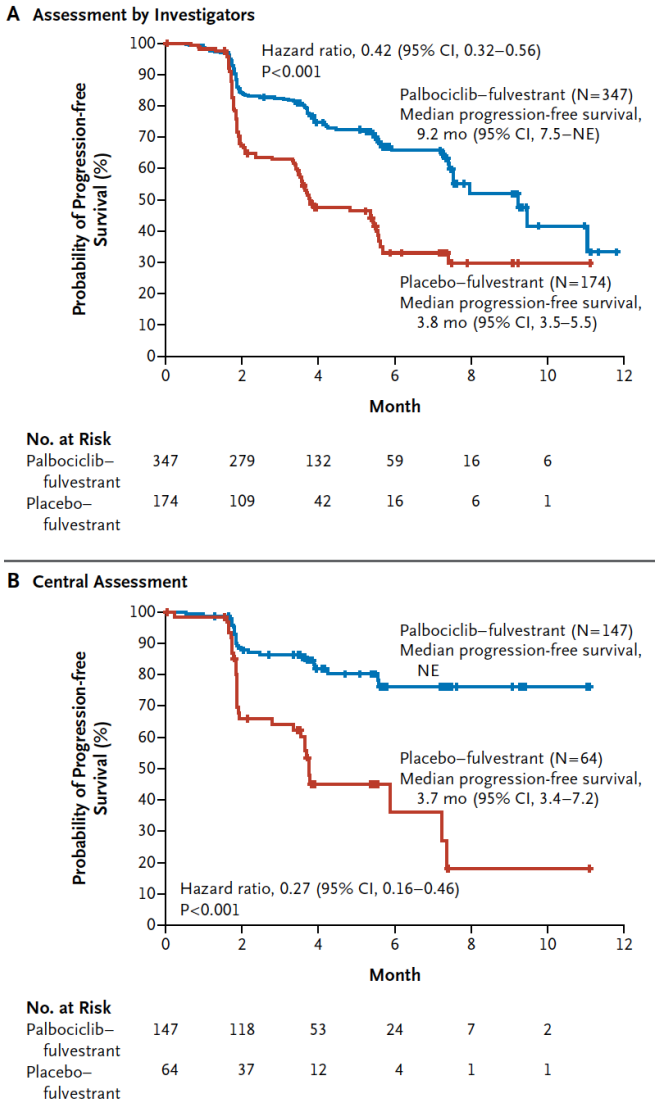
PALOMA -3

≥2° line
palbociclib+fulvestrant vs.
placebo+fulvestrant

PRIMARY ENDPOINT: Phase III : progression free survival (time frame: baseline up to 10 mo)

PALOMA -3

≥2° line palbociclib+fulvestrant vs. placebo+fulvestrant

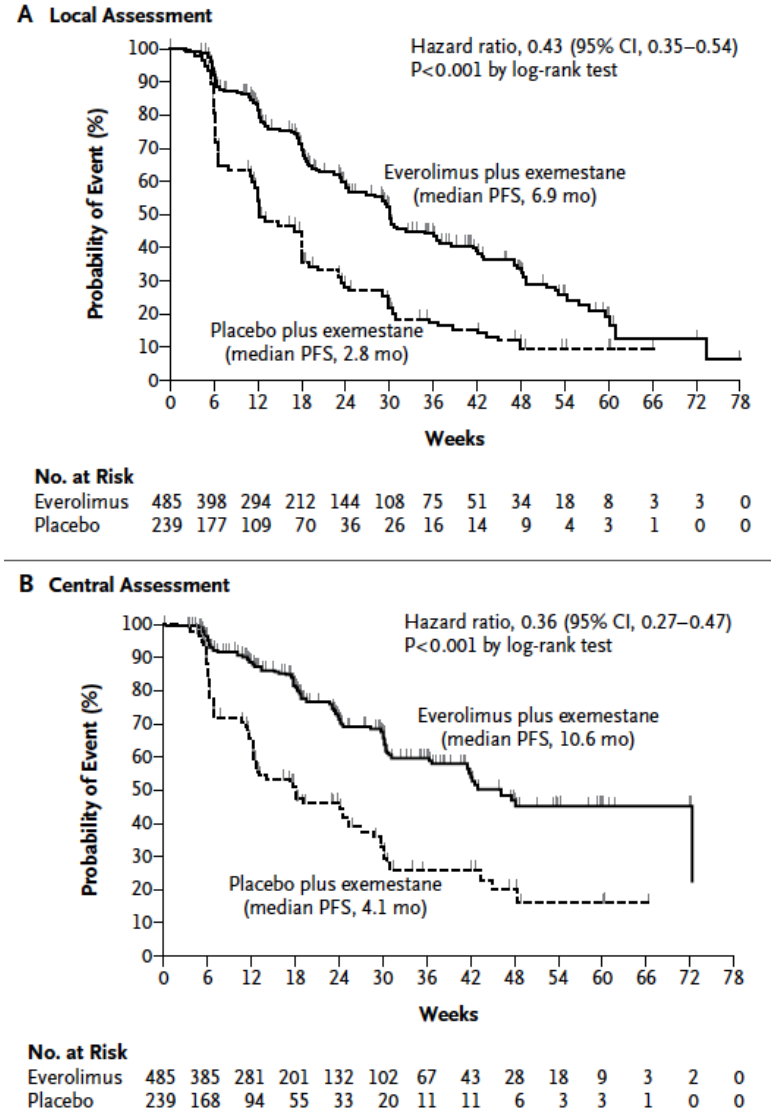


- Imaging (CT, MRI, or both) was performed at screening within 4 weeks before randomization then repeated **every 8+1** weeks until progression
- Measurable disease according to RECIST 1.1 or bone-only lytic of mixed lesions assessable by CT or MRI
- **Blinded review: 211 pts (40%)**

BOLERO -2

≥2° line
Everolimus+exemestane vs. placebo+exemestane

- Imaging (CT, MRI, or both) was performed at screening then repeated **every 6 weeks** until progression
- Measurable disease or mainly lytic bone disease assessable by CT or MRI
- **Central review: 724 pts (100%)**



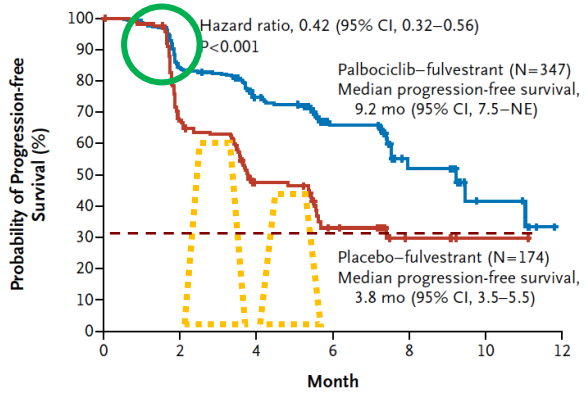
PALOMA -3

≥2° line palbociclib+fulvestrant vs. placebo+fulvestrant

BOLERO -2

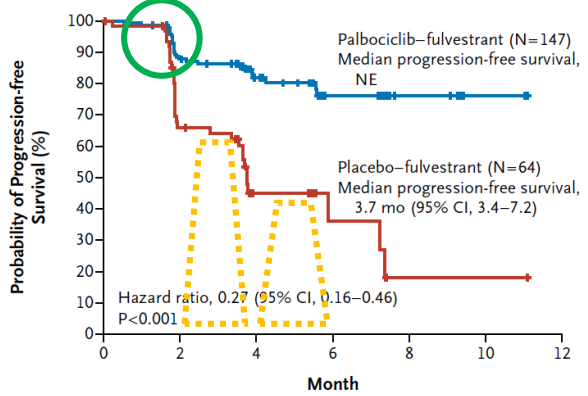
≥2° line Everolimus+exemestane vs. placebo+exemestane

A Assessment by Investigators



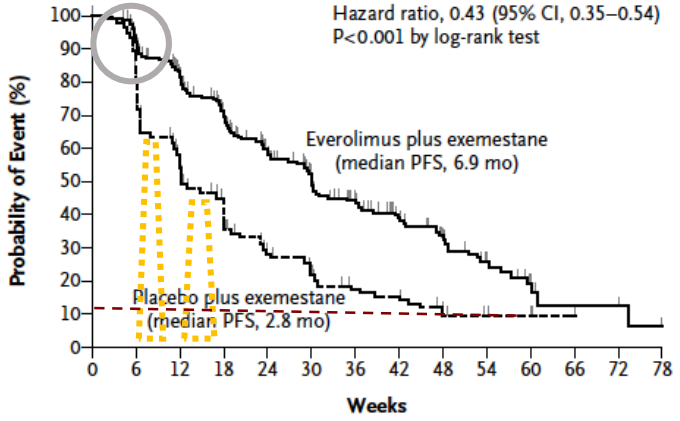
No. at Risk						
Palbociclib–fulvestrant	347	279	132	59	16	6
Placebo–fulvestrant	174	109	42	16	6	1

B Central Assessment



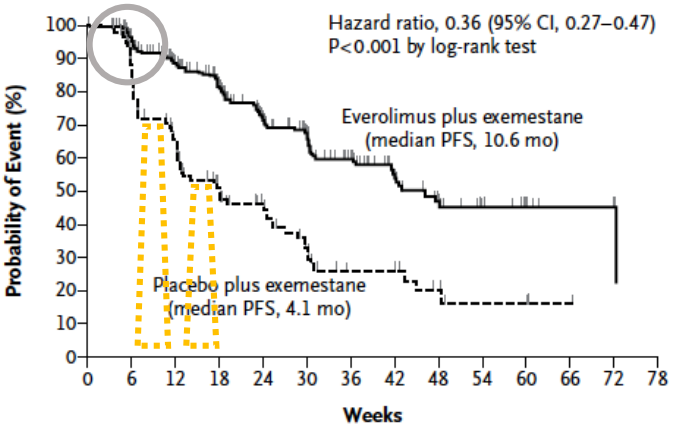
No. at Risk						
Palbociclib–fulvestrant	147	118	53	24	7	2
Placebo–fulvestrant	64	37	12	4	1	1

A Local Assessment



No. at Risk													
Everolimus	485	398	294	212	144	108	75	51	34	18	8	3	3	0
Placebo	239	177	109	70	36	26	16	14	9	4	3	1	0	0

B Central Assessment



No. at Risk													
Everolimus	485	385	281	201	132	102	67	43	28	18	9	3	2	0
Placebo	239	168	94	55	33	20	11	11	6	3	3	1	0	0

Clinicians could easily guess which patient was not receiving

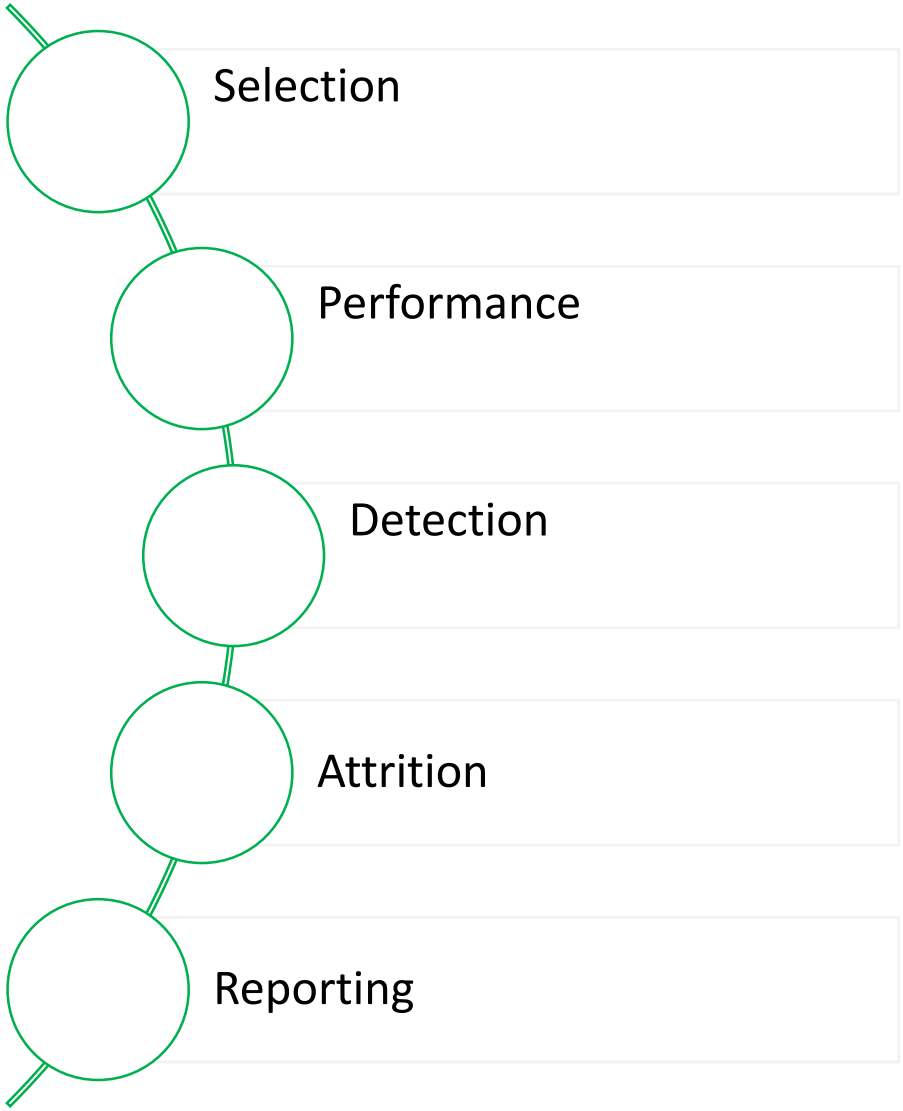
- Palbociclib

(e.g. through absence of neutropenia; 78.8% vs 3.5%)

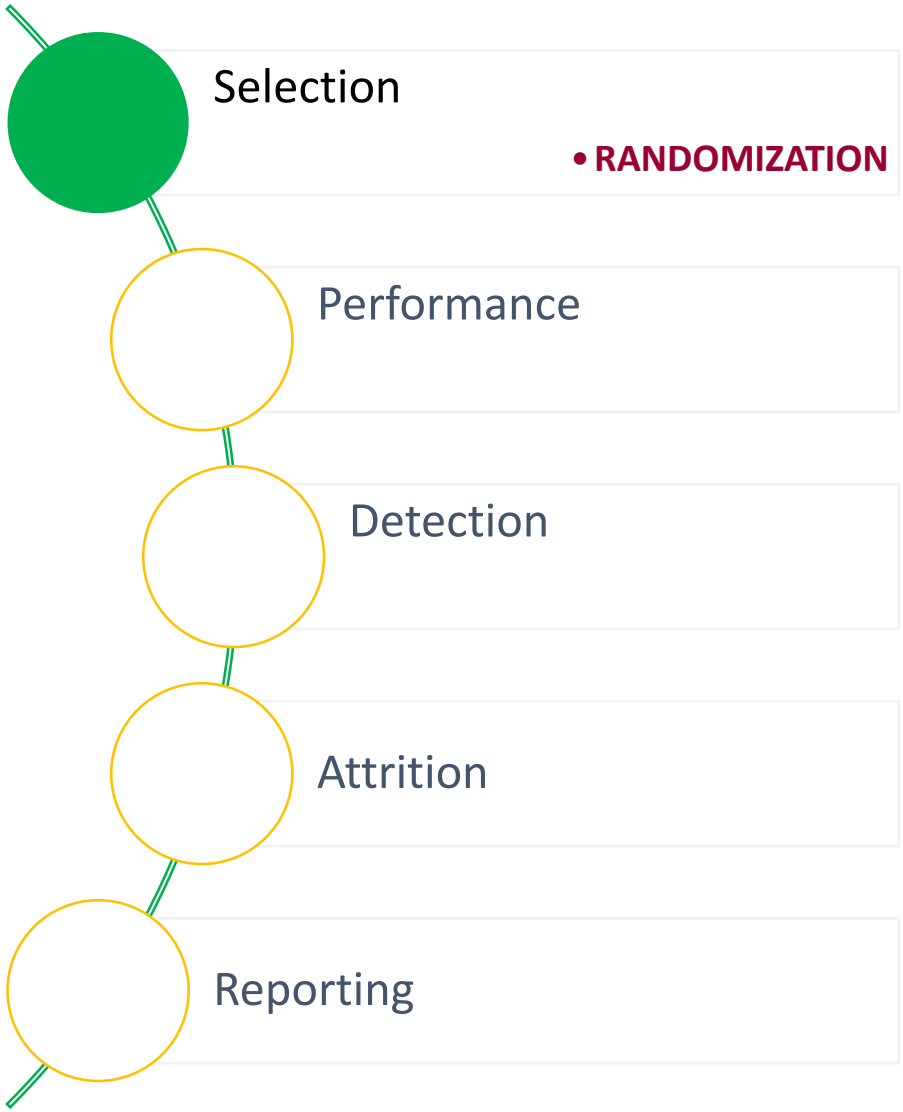
- Everolimus

(e.g. through absence of stomatitis; 56% vs 11%);

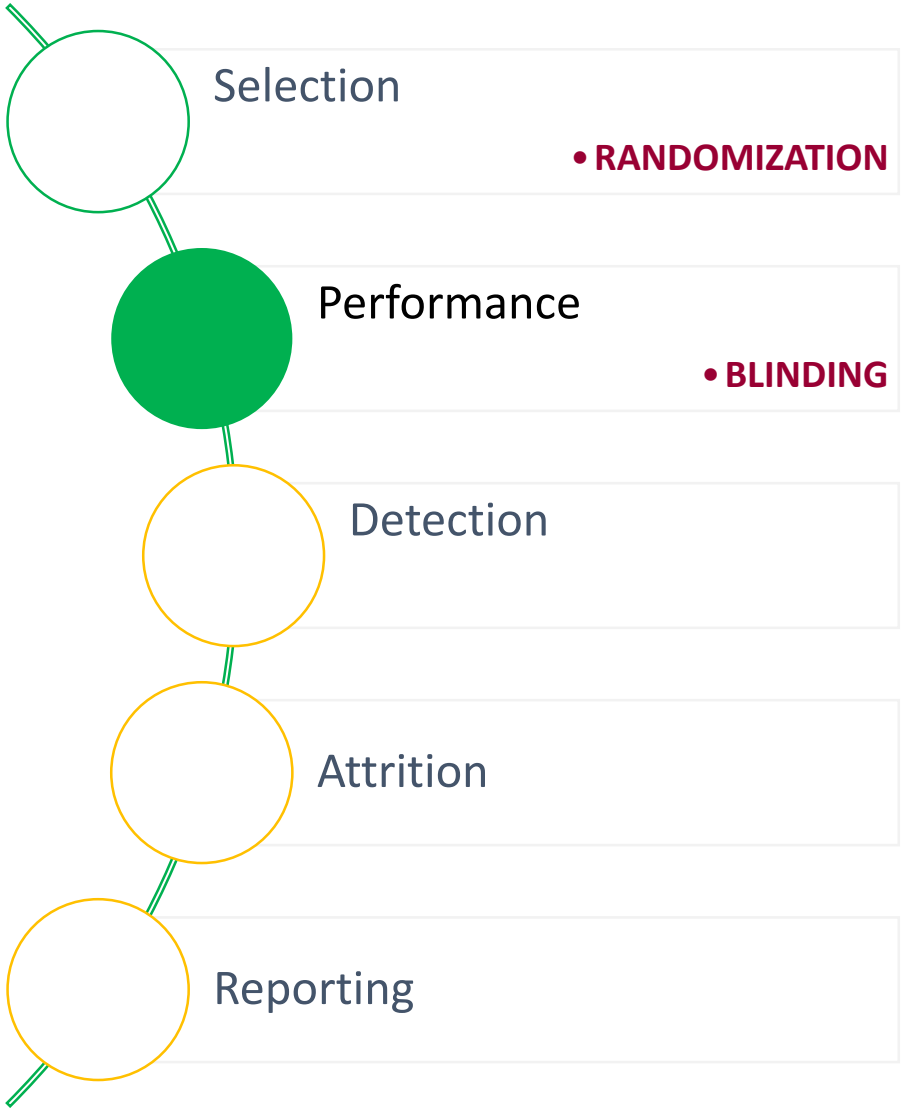
BIAS



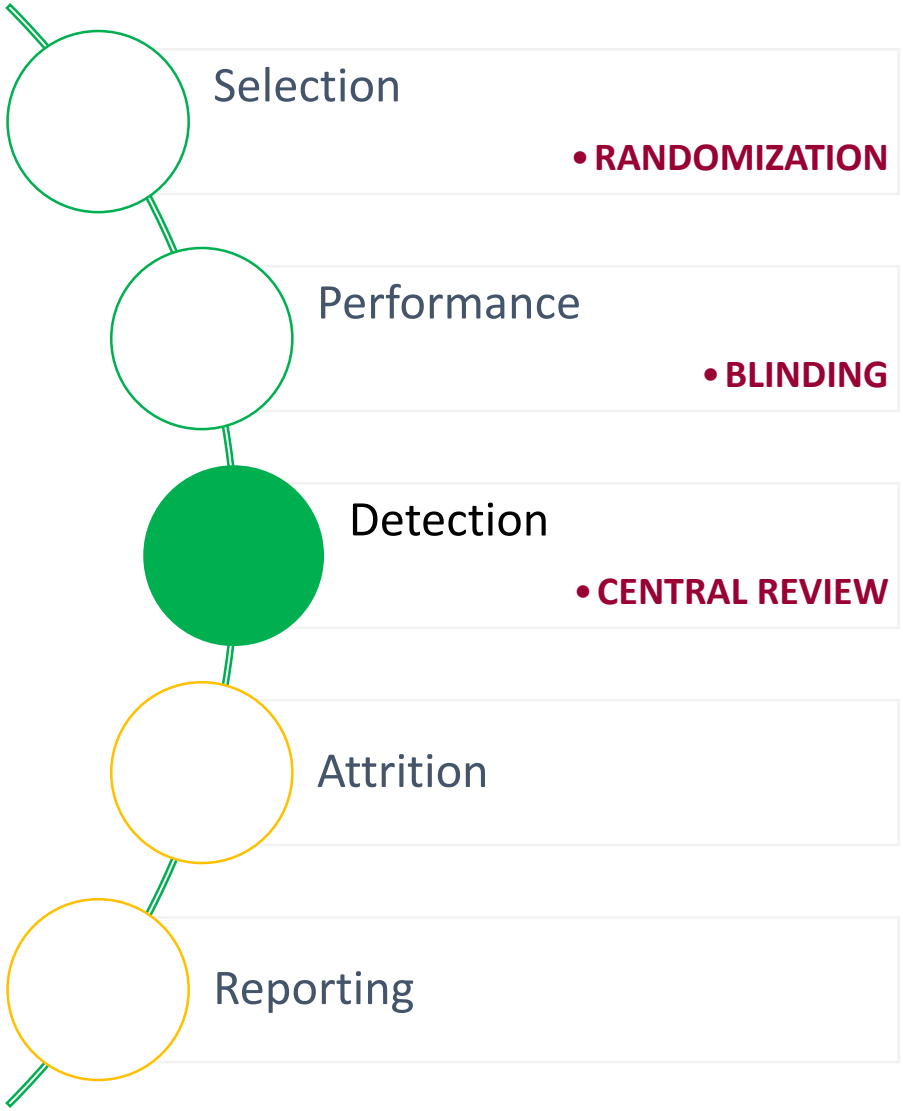
BIAS


Selection
• RANDOMIZATION
Performance
Detection
Attrition
Reporting

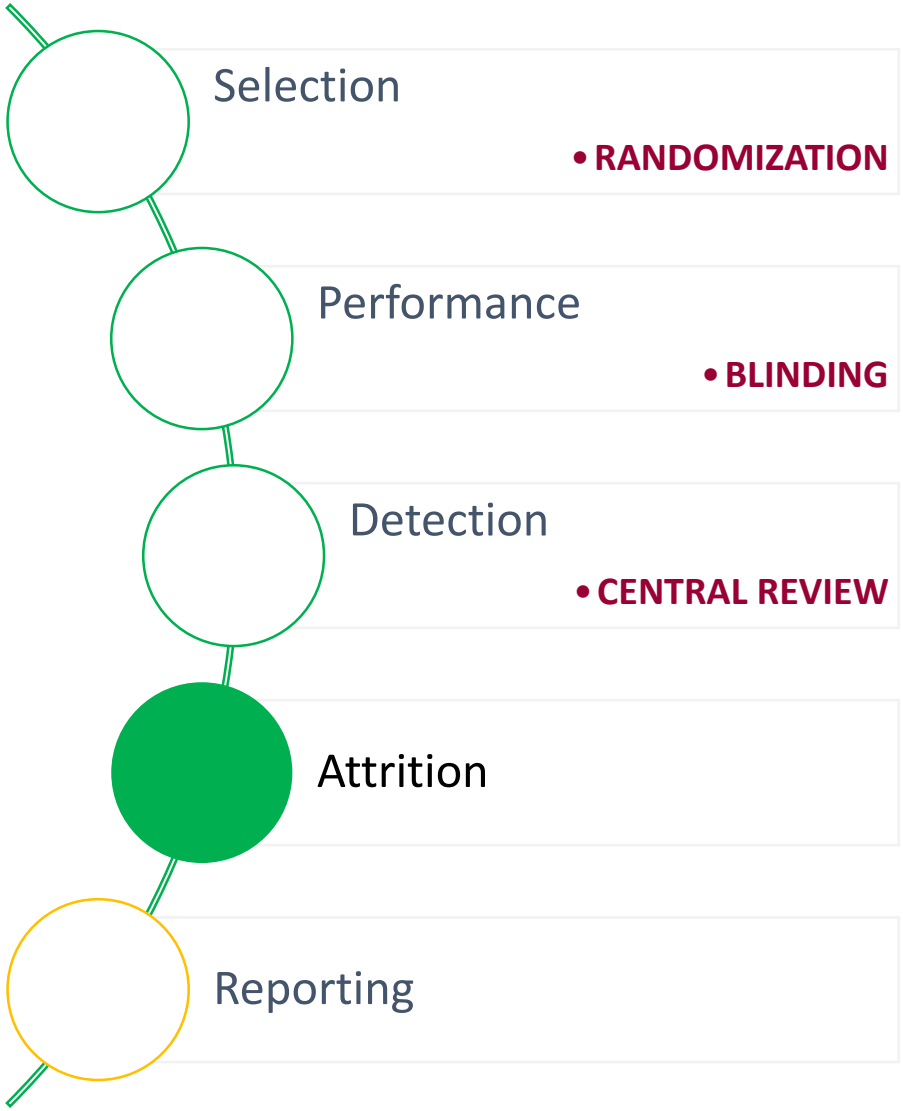
BIAS


Selection
• RANDOMIZATION
Performance
• BLINDING
Detection
Attrition
Reporting

BIAS

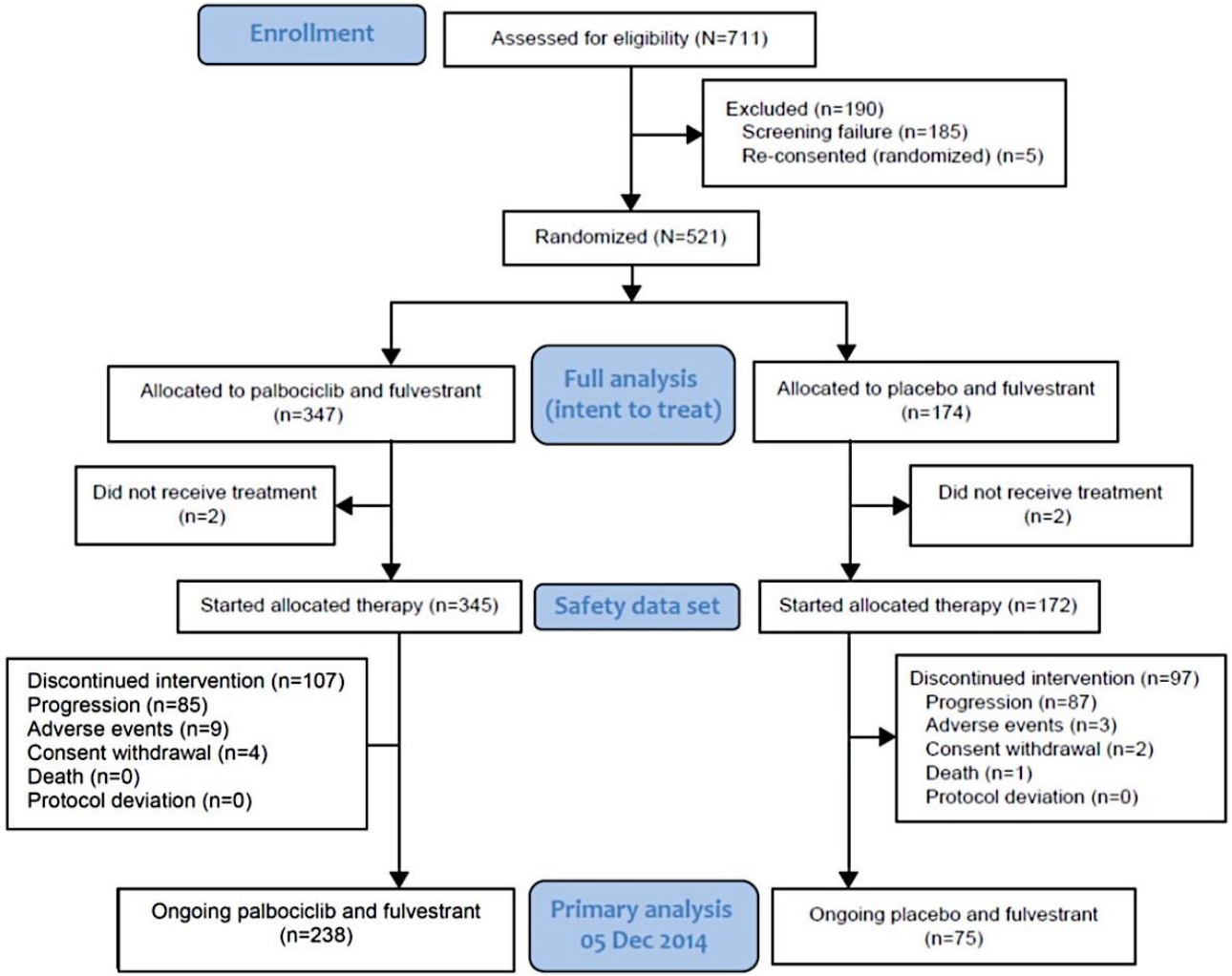

Selection
• RANDOMIZATION
Performance
• BLINDING
Detection
• CENTRAL REVIEW
Attrition
Reporting

BIAS


Selection
• RANDOMIZATION
Performance
• BLINDING
Detection
• CENTRAL REVIEW
Attrition
Reporting

PALOMA -3

≥2° line palbociclib+fulvestrant vs. placebo+fulvestrant



- OPPORTUNITIES
- OBJECTIVES
- DESIGN
- ENDPOINTS
- **POPULATION**
- RESULTS
- CONSIDERATIONS

PALOMA -3

≥2° line
palbociclib+fulvestrant vs.
placebo+fulvestrant

HR–positive,
HER2-negative,
advanced breast cancer (ABC)
Pre/peri* or post-menopausal women

≤ 1 prior chemotherapy regimen for ABC

(N = 521)

2:1

Palbociclib 125 mg daily , 3 wks on/1 wk off
+ Fulvestrant 500 mg q4w
(n = 347)

Placebo 3 wks on/1 wk off
+ Fulvestrant 500 mg q4w
(n = 174)

- Stratification
  - Sensitivity to previous hormonal therapy
  - Presence of visceral disease
  - Menopausal status at study entry

Refractory to therapy

- Recurrence during or within
  12 mos of end of adjuvant treatment
- Progression during or within
  1 mo after end of treatment for advanced disease

Sensitivity to previous therapy

- relapse after 24 months of adjuvant endocrine therapy
- clinical benefit (objective response [complete or partial] or stable disease lasting ≥24 weeks) from prior endocrine therapy in the context of advanced disease.

PALOMA -3

≥2° line palbociclib+fulvestrant vs. placebo+fulvestrant

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

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

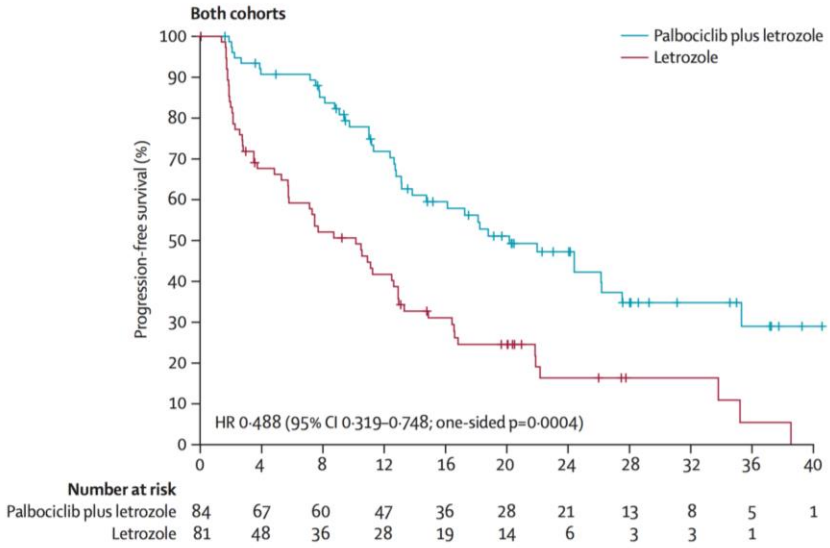
	PALOMA -3		BOLERO -2	
	palbociclib+ fulvestrant	placebo+ fulvestrant	Everolimus+ exemestane	placebo+ exemestane
Visceral disease				
yes	56	56	59.4	60.3
Prior lines of therapy in the contest of metastatic disease				
0	24.2	25.9	-	-
1	38	40.2	16	18
2	25.9	24.7	30	30
≥3	11.8	9.2	54	53

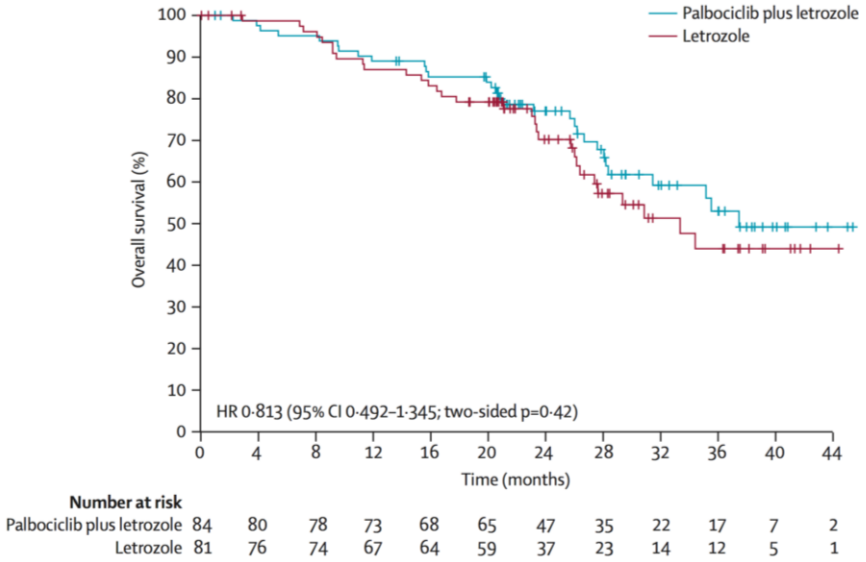
	PALOMA -3		BOLERO -2	
	palbociclib+ fulvestrant	placebo+ fulvestrant	Everolimus+ exemestane	placebo+ exemestane
Visceral disease				
yes	56	56	59.4	60.3
Prior lines of therapy in the contest of metastatic disease				
0	24.2	25.9	-	-
1	38	40.2	16	18
2	25.9	24.7	30	30
≥3	11.8	9.2	54	53

- OPPORTUNITIES
- OBJECTIVES
- DESIGN
- ENDPOINTS
- POPULATION
- **RESULTS**
- CONSIDERATIONS

PALOMA -1

1° line
palbociclib+letrozole
vs. letrozole

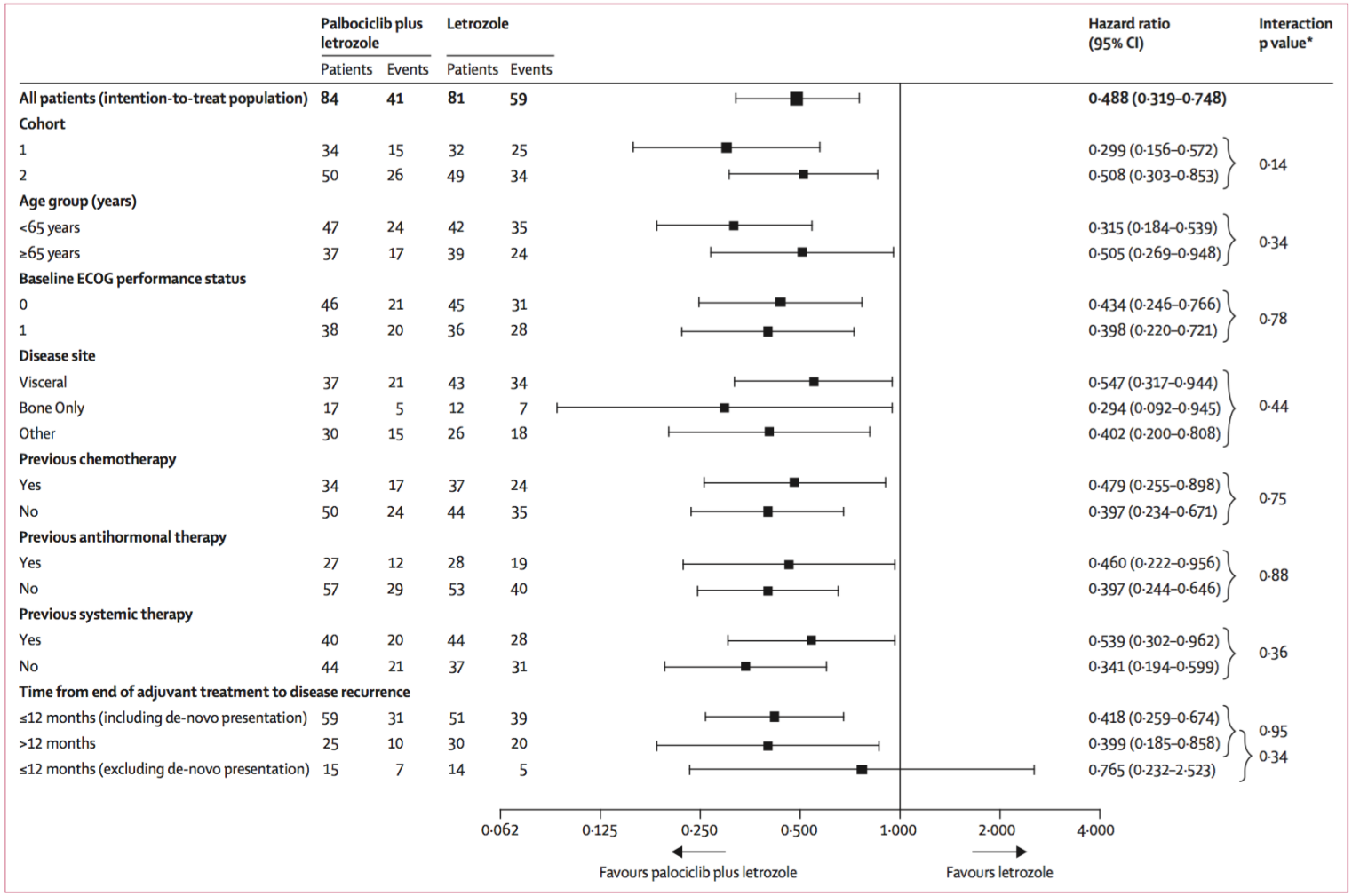




	PFS (months)	OS (months)
Palbociclib+letrozole	**20.2** (13.8-27.5)	**37.5** (95% CI 28.4–NE; 30 events)
letrozole	10.2 (95% CI 5.7-12.6)	33.3 (26.4–NE; 31 events)

PALOMA -1

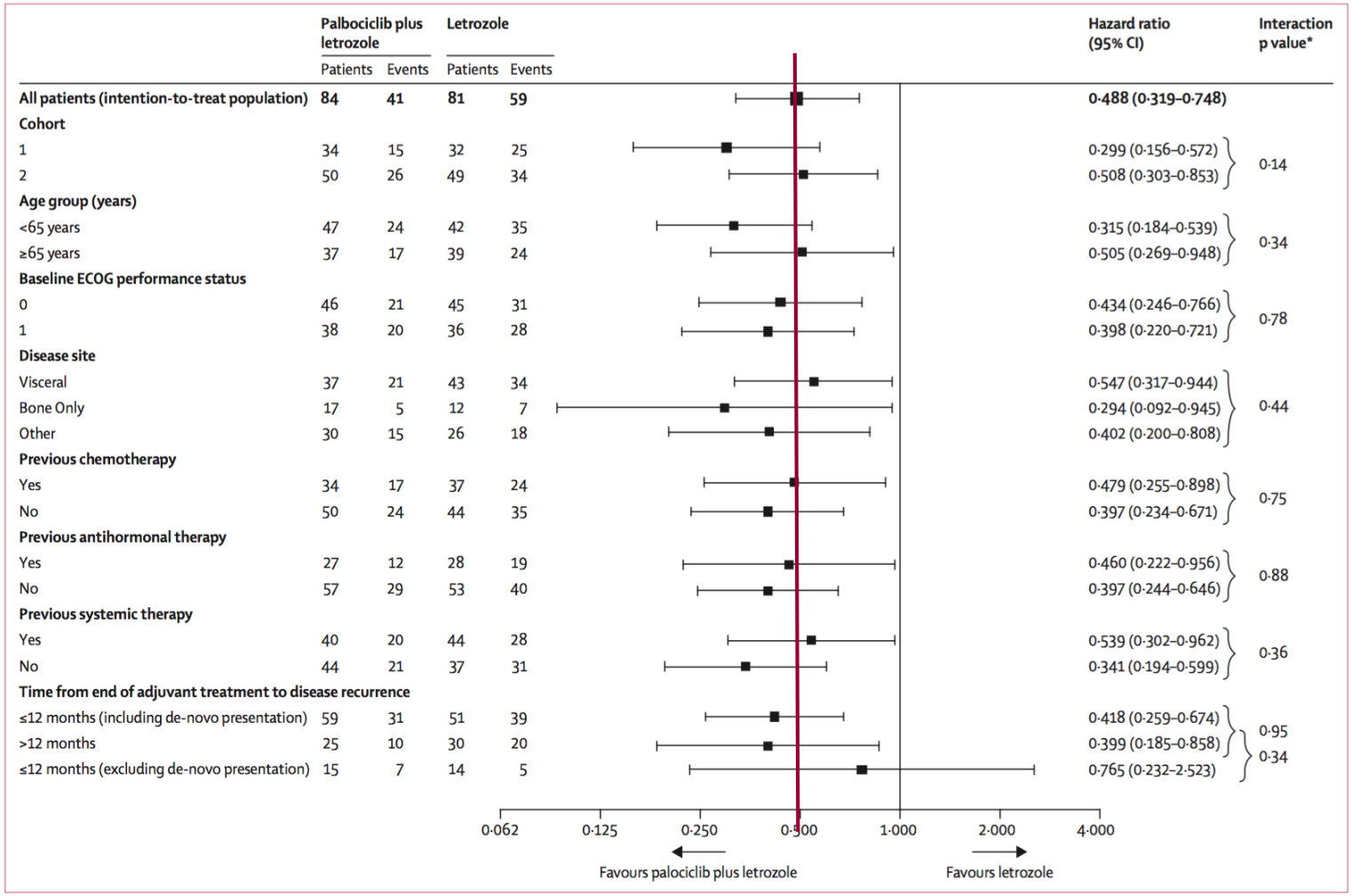
1° line
palbociclib+letrozole
vs. letrozole



	Palbociclib plus letrozole		Letrozole		Hazard ratio (95% CI)	Interaction p value*
	Patients	Events	Patients	Events		
All patients (intention-to-treat population)	**84**	**41**	**81**	**59**	**0·488 (0·319–0·748)**	
Cohort						
1	34	15	32	25	0·299 (0·156–0·572)	0·14
2	50	26	49	34	0·508 (0·303–0·853)	
Age group (years)						
<65 years	47	24	42	35	0·315 (0·184–0·539)	0·34
≥65 years	37	17	39	24	0·505 (0·269–0·948)	
Baseline ECOG performance status						
0	46	21	45	31	0·434 (0·246–0·766)	0·78
1	38	20	36	28	0·398 (0·220–0·721)	
Disease site						
Visceral	37	21	43	34	0·547 (0·317–0·944)	0·44
Bone Only	17	5	12	7	0·294 (0·092–0·945)	
Other	30	15	26	18	0·402 (0·200–0·808)	
Previous chemotherapy						
Yes	34	17	37	24	0·479 (0·255–0·898)	0·75
No	50	24	44	35	0·397 (0·234–0·671)	
Previous antihormonal therapy						
Yes	27	12	28	19	0·460 (0·222–0·956)	0·88
No	57	29	53	40	0·397 (0·244–0·646)	
Previous systemic therapy						
Yes	40	20	44	28	0·539 (0·302–0·962)	0·36
No	44	21	37	31	0·341 (0·194–0·599)	
Time from end of adjuvant treatment to disease recurrence						
≤12 months (including de-novo presentation)	59	31	51	39	0·418 (0·259–0·674)	0·95
>12 months	25	10	30	20	0·399 (0·185–0·858)	
≤12 months (excluding de-novo presentation)	15	7	14	5	0·765 (0·232–2·523)	0·34

PALOMA -1

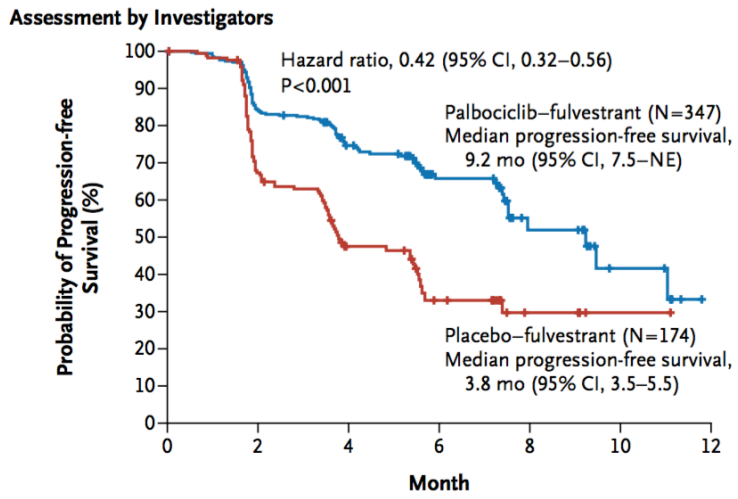
1° line
palbociclib+letrozole
vs. letrozole

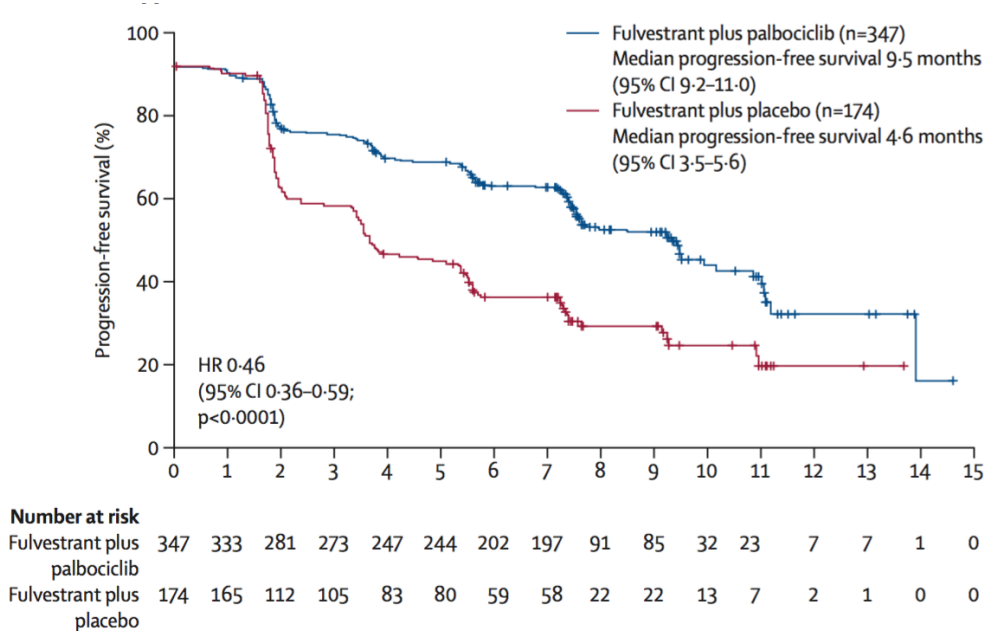


	Palbociclib plus letrozole		Letrozole		Hazard ratio (95% CI)	Interaction p value*
	Patients	Events	Patients	Events		
All patients (intention-to-treat population)	**84**	**41**	**81**	**59**	**0·488 (0·319–0·748)**	
Cohort						
1	34	15	32	25	0·299 (0·156–0·572)	0·14
2	50	26	49	34	0·508 (0·303–0·853)	
Age group (years)						
<65 years	47	24	42	35	0·315 (0·184–0·539)	0·34
≥65 years	37	17	39	24	0·505 (0·269–0·948)	
Baseline ECOG performance status						
0	46	21	45	31	0·434 (0·246–0·766)	0·78
1	38	20	36	28	0·398 (0·220–0·721)	
Disease site						
Visceral	37	21	43	34	0·547 (0·317–0·944)	0·44
Bone Only	17	5	12	7	0·294 (0·092–0·945)	
Other	30	15	26	18	0·402 (0·200–0·808)	
Previous chemotherapy						
Yes	34	17	37	24	0·479 (0·255–0·898)	0·75
No	50	24	44	35	0·397 (0·234–0·671)	
Previous antihormonal therapy						
Yes	27	12	28	19	0·460 (0·222–0·956)	0·88
No	57	29	53	40	0·397 (0·244–0·646)	
Previous systemic therapy						
Yes	40	20	44	28	0·539 (0·302–0·962)	0·36
No	44	21	37	31	0·341 (0·194–0·599)	
Time from end of adjuvant treatment to disease recurrence						
≤12 months (including de-novo presentation)	59	31	51	39	0·418 (0·259–0·674)	0·95
>12 months	25	10	30	20	0·399 (0·185–0·858)	0·34
≤12 months (excluding de-novo presentation)	15	7	14	5	0·765 (0·232–2·523)	

PALOMA -3

≥2° line palbociclib+fulvestrant vs. placebo+fulvestrant





Main assumption:

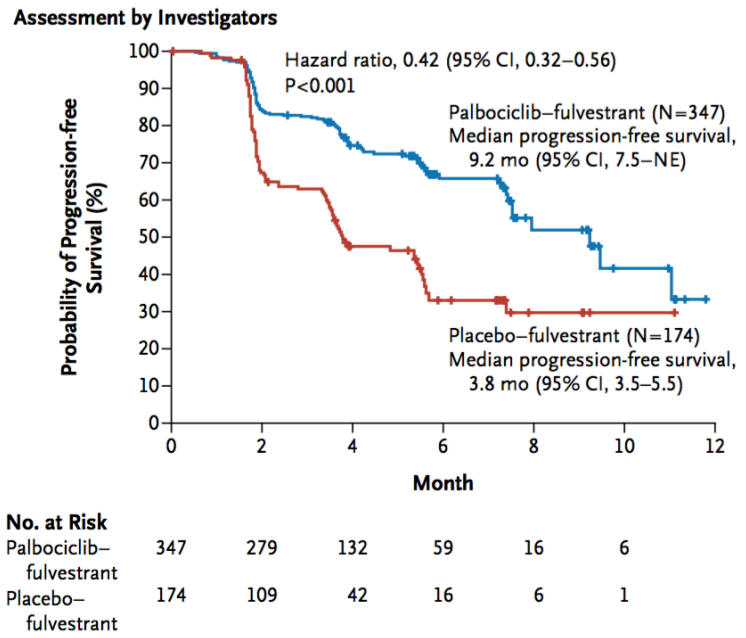
238 PFS events to have 90% power to detect a hazard ratio of 0.64

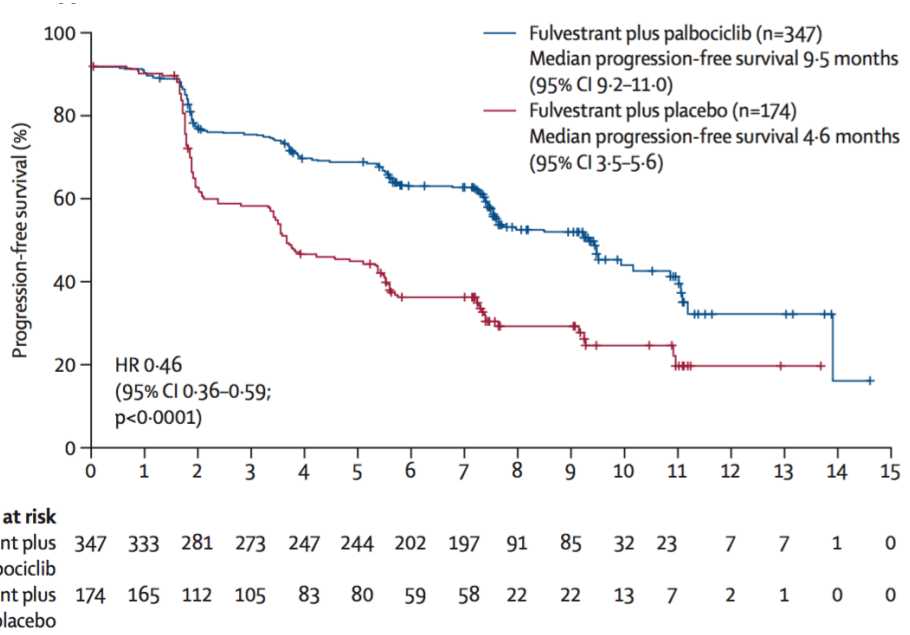
56% increase in median PFS → 6 months vs. 9.4 months

with a one-side significance level of α=0.025

PALOMA -3

≥2° line palbociclib+fulvestrant vs. placebo+fulvestrant



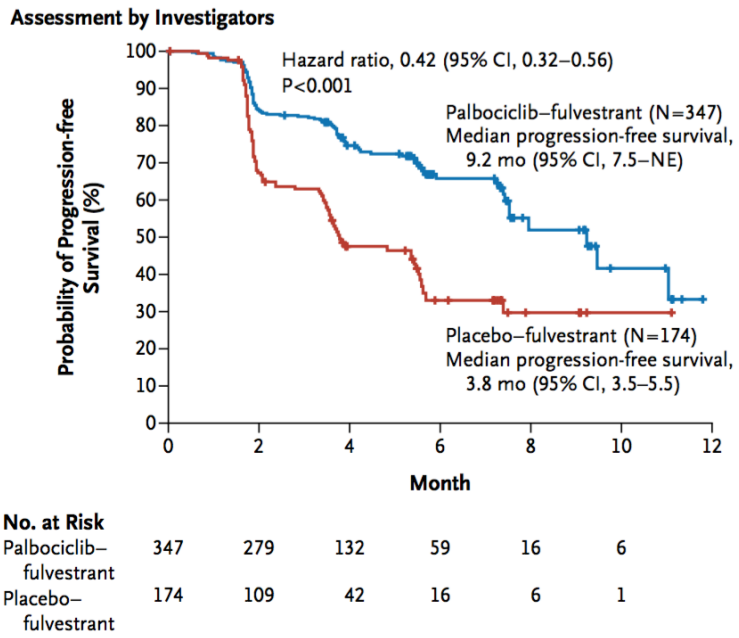


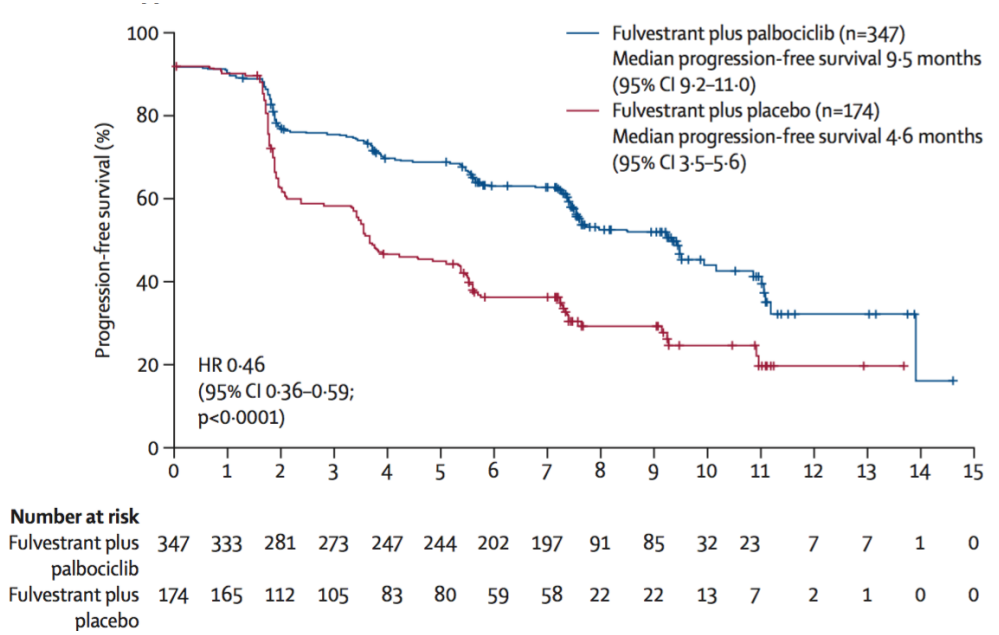
What about COMPARATOR?

CONFIRM (fulvestrant 500 mg)	PFS (mo)	OS (mo)
ALL pts	6.5	26.4
AE subgroup (n=423)	8.6	30.6
AI subgroup (n=313)	5.4	24.1

PALOMA -3

≥2° line palbociclib+fulvestrant vs. placebo+fulvestrant





What about COMPARATOR?

CONFIRM (fulvestrant 500 mg)	PFS (mo)	OS (mo)
ALL pts	6.5	26.4
AE subgroup (n=423)	8.6	30.6
AI subgroup (n=313)	5.4	24.1

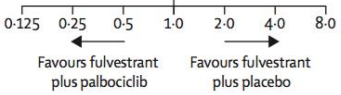
Exclusion criteria: *"[…] more than one chemotherapy or endocrine therapy for advanced disease. […]"*

	PALOMA -3	BOLERO -2
Age, median (years)	57	62
Pre-/peri-menopausal	20.7%	0%
Visceral disease	59.7%	56%
≥ 3 sites of disease	38.9%	36%
≥ 3 lines of therapy	10.9%	54%
Previous chemotherapy for advanced disease	30.8%	26%
Previous sensitivity to endocrine therapy	79%	84%
PFS, months	9.2 vs 3.8 HR 0.42, p<.001	6.9 vs 2.8 HR 0.43, p<.001
OS, months	-	31 vs 26.6 HR 0.89, p=0.14

PALOMA -3

≥2° line palbociclib+fulvestrant vs. placebo+fulvestrant

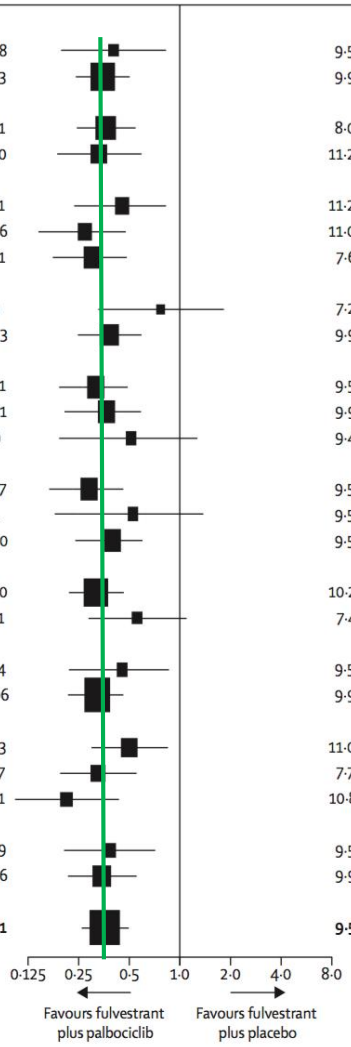
	Fulvestrant plus palbociclib (events [n]/ patients)	Fulvestrant plus placebo (events [n]/ patients)	Events (n)/ patients	Fulvestrant plus palbociclib median progression-free survival (95%CI)	Fulvestrant plus placebo median progression-free survival (95%CI)	Hazard ratio (95% CI)	$p_{interaction}$
Menopausal status at study entry							0·89
Premenopausal or perimenopausal	30/72	23/36	53/108	9·5 (7·4–NE)	5·6 (1·8–7·6)	0·50 (0·29–0·87)	
Postmenopausal	115/275	91/138	206/413	9·9 (8·5–11·0)	3·9 (3·5–5·5)	0·45 (0·34–0·59)	
Site of metastatic disease							0·82
Visceral	101/206	76/105	177/311	8·0 (7·5–9·5)	3·5 (2·0–5·3)	0·47 (0·34–0·63)	
Non-visceral	44/141	38/69	82/210	11·2 (9·9–NE)	5·6 (4·6–10·9)	0·43 (0·28–0·67)	
Number of disease sites							0·43
1	36/111	29/60	65/171	11·2 (9·9–NE)	9·3 (5·5–NE)	0·55 (0·34–0·90)	
2	40/95	36/51	76/146	11·0 (7·5–NE)	3·6 (1·9–5·6)	0·37 (0·24–0·59)	
≥3	69/139	49/62	118/201	7·6 (7·4–9·5)	3·4 (1·9–3·7)	0·40 (0·28–0·59)	
Disease-free interval							0·16
≤24 months	24/41	15/22	39/63	7·2 (2·5–9·2)	5·4 (1·8–9·3)	0·83 (0·43–1·59)	
>24 months	77/192	63/101	140/293	9·9 (9·3–11·2)	5·5 (3·5–7·3)	0·48 (0·35–0·68)	
Previous lines of endocrine therapy							0·75
1	63/160	58/91	121/251	9·5 (7·6–NE)	4·6 (3·4–5·6)	0·42 (0·29–0·60)	
2	61/140	44/61	105/201	9·9 (7·5–13·9)	5·1 (2·8–7·2)	0·46 (0·31–0·69)	
≥3	21/47	12/22	33/69	9·4 (7·5–NE)	3·9 (1·8–NE)	0·61 (0·30–1·24)	
Previous endocrine therapy							0·63
Aromatase inhibitor only	58/137	50/70	108/207	9·5 (7·6–13·9)	3·7 (2·1–5·5)	0·39 (0·27–0·57)	
Tamoxifen only	18/51	10/23	28/74	9·5 (7·5–NE)	NE (1·7–NE)	0·61 (0·28–1·33)	
Aromatase inhibitor and tamoxifen	69/159	54/81	123/240	9·5 (7·6–11·2)	4·2 (3·5–7·2)	0·50 (0·35–0·71)	
Sensitivity to previous hormonal therapy							0·13
Yes	108/274	89/136	197/410	10·2 (9·4–11·2)	4·2 (3·5–5·6)	0·42 (0·32–0·56)	
No	37/73	25/38	62/111	7·4 (5·6–9·2)	5·4 (1·9–7·4)	0·64 (0·39–1·07)	
The purpose of most recent therapy							0·39
Neoadjuvant or adjuvant treatment	34/74	24/40	58/114	9·5 (7·4–NE)	5·4 (2·1–10·9)	0·55 (0·32–0·92)	
Metastatic treatment	111/273	90/133	201/406	9·9 (9·2–11·2)	3·9 (3·5–5·6)	0·43 (0·32–0·57)	
Previous chemotherapy							0·22
Neoadjuvant or adjuvant treatment only	59/139	43/74	102/213	11·0 (7·6–NE)	5·6 (3·5–9·3)	0·60 (0·40–0·88)	
Metastatic treatment	53/113	47/64	100/177	7·7 (5·7–9·5)	3·5 (1·9–5·4)	0·43 (0·29–0·64)	
None	33/95	24/36	57/131	10·8 (9·5–NE)	5·4 (3·4–7·3)	0·31 (0·18–0·53)	
PIK3CA status							0·83
Positive	41/85	31/44	72/129	9·5 (5·7–11·2)	3·6 (1·9–5·6)	0·48 (0·30–0·78)	
Negative	71/180	56/86	127/266	9·9 (9·2–13·9)	4·6 (3·4–7·3)	0·45 (0·31–0·64)	
Overall	**145/347**	**114/174**	**259/521**	**9·5 (9·2–11·0)**	**4·6 (3·5–5·6)**	**0·46 (0·36–0·59)**	



PALOMA -3

≥2° line
palbociclib+fulvestrant vs.
placebo+fulvestrant

	Fulvestrant plus palbociclib (events [n]/ patients)	Fulvestrant plus placebo (events [n]/ patients)	Events (n)/ patients	Fulvestrant plus palbociclib median progression-free survival (95%CI)	Fulvestrant plus placebo median progression-free survival (95%CI)	Hazard ratio (95% CI)	$p_{interaction}$
Menopausal status at study entry							0·89
Premenopausal or perimenopausal	30/72	23/36	53/108	9·5 (7·4–NE)	5·6 (1·8–7·6)	0·50 (0·29–0·87)	
Postmenopausal	115/275	91/138	206/413	9·9 (8·5–11·0)	3·9 (3·5–5·5)	0·45 (0·34–0·59)	
Site of metastatic disease							0·82
Visceral	101/206	76/105	177/311	8·0 (7·5–9·5)	3·5 (2·0–5·3)	0·47 (0·34–0·63)	
Non-visceral	44/141	38/69	82/210	11·2 (9·9–NE)	5·6 (4·6–10·9)	0·43 (0·28–0·67)	
Number of disease sites							0·43
1	36/111	29/60	65/171	11·2 (9·9–NE)	9·3 (5·5–NE)	0·55 (0·34–0·90)	
2	40/95	36/51	76/146	11·0 (7·5–NE)	3·6 (1·9–5·6)	0·37 (0·24–0·59)	
≥3	69/139	49/62	118/201	7·6 (7·4–9·5)	3·4 (1·9–3·7)	0·40 (0·28–0·59)	
Disease-free interval							0·16
≤24 months	24/41	15/22	39/63	7·2 (2·5–9·2)	5·4 (1·8–9·3)	0·83 (0·43–1·59)	
>24 months	77/192	63/101	140/293	9·9 (9·3–11·2)	5·5 (3·5–7·3)	0·48 (0·35–0·68)	
Previous lines of endocrine therapy							0·75
1	63/160	58/91	121/251	9·5 (7·6–NE)	4·6 (3·4–5·6)	0·42 (0·29–0·60)	
2	61/140	44/61	105/201	9·9 (7·5–13·9)	5·1 (2·8–7·2)	0·46 (0·31–0·69)	
≥3	21/47	12/22	33/69	9·4 (7·5–NE)	3·9 (1·8–NE)	0·61 (0·30–1·24)	
Previous endocrine therapy							0·63
Aromatase inhibitor only	58/137	50/70	108/207	9·5 (7·6–13·9)	3·7 (2·1–5·5)	0·39 (0·27–0·57)	
Tamoxifen only	18/51	10/23	28/74	9·5 (7·5–NE)	NE (1·7–NE)	0·61 (0·28–1·33)	
Aromatase inhibitor and tamoxifen	69/159	54/81	123/240	9·5 (7·6–11·2)	4·2 (3·5–7·2)	0·50 (0·35–0·71)	
Sensitivity to previous hormonal therapy							0·13
Yes	108/274	89/136	197/410	10·2 (9·4–11·2)	4·2 (3·5–5·6)	0·42 (0·32–0·56)	
No	37/73	25/38	62/111	7·4 (5·6–9·2)	5·4 (1·9–7·4)	0·64 (0·39–1·07)	
The purpose of most recent therapy							0·39
Neoadjuvant or adjuvant treatment	34/74	24/40	58/114	9·5 (7·4–NE)	5·4 (2·1–10·9)	0·55 (0·32–0·92)	
Metastatic treatment	111/273	90/133	201/406	9·9 (9·2–11·2)	3·9 (3·5–5·6)	0·43 (0·32–0·57)	
Previous chemotherapy							0·22
Neoadjuvant or adjuvant treatment only	59/139	43/74	102/213	11·0 (7·6–NE)	5·6 (3·5–9·3)	0·60 (0·40–0·88)	
Metastatic treatment	53/113	47/64	100/177	7·7 (5·7–9·5)	3·5 (1·9–5·4)	0·43 (0·29–0·64)	
None	33/95	24/36	57/131	10·8 (9·5–NE)	5·4 (3·4–7·3)	0·31 (0·18–0·53)	
PIK3CA status							0·83
Positive	41/85	31/44	72/129	9·5 (5·7–11·2)	3·6 (1·9–5·6)	0·48 (0·30–0·78)	
Negative	71/180	56/86	127/266	9·9 (9·2–13·9)	4·6 (3·4–7·3)	0·45 (0·31–0·64)	
Overall	**145/347**	**114/174**	**259/521**	**9·5 (9·2–11·0)**	**4·6 (3·5–5·6)**	**0·46 (0·36–0·59)**	



- OPPORTUNITIES
- OBJECTIVES
- DESIGN
- ENDPOINTS
- POPULATION
- RESULTS
- **CONSIDERATIONS**

PALOMA -1

1° line
palbociclib+letrozole
vs. letrozole

- **Phase II is a phase II**

PALOMA -3

≥2° line
palbociclib+fulvestrant vs.
placebo+fulvestrant

- Phase III is a phase III
  - INTERNAL VALIDITY and EXTERNAL VALIDITY
    - Imprecision: not serious
    - Risk of bias: not serious
      - Blinding and central review
    - Inconsistency:
      - Primary endpoint
        - PFS or OS
    - Indirectness:
      - comparator arm
        - Palbociclib: CT or not CT?

The end