Inibitori delle chinasi –ciclino dipendenti nel trattamento della malattia metastatica HR-positiva

Gli studi clinici

Laura Orlando
UOC Oncologia & Breast Unit
Brindisi

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Summary

- **Studi con Palbociclib**

+ AI: **Paloma 1** (Fase II, Lancet Oncol 2015)
+ AI: Paloma 2 (Fase III ongoing)
+ Fulv**: Paloma 3** (Fase III, NEJM 2015-Interim analysis, Lancet Oncol 2016-final analysis)

- **Studi con Abemaciclib**

+ AI: Monarch-3 (Fase III ongoing)
+ Fulv: Monarch-2 (Fase III ongoing)

- **Studi Con Ribocliclib**

+ AI: Monaleesa-2 (fase III ongoing)
+ Fulv: Monaleesa-3 (fase III ongoing)
+ Tam–LHRH: Monaleesa-7 (Fase III ongoing)

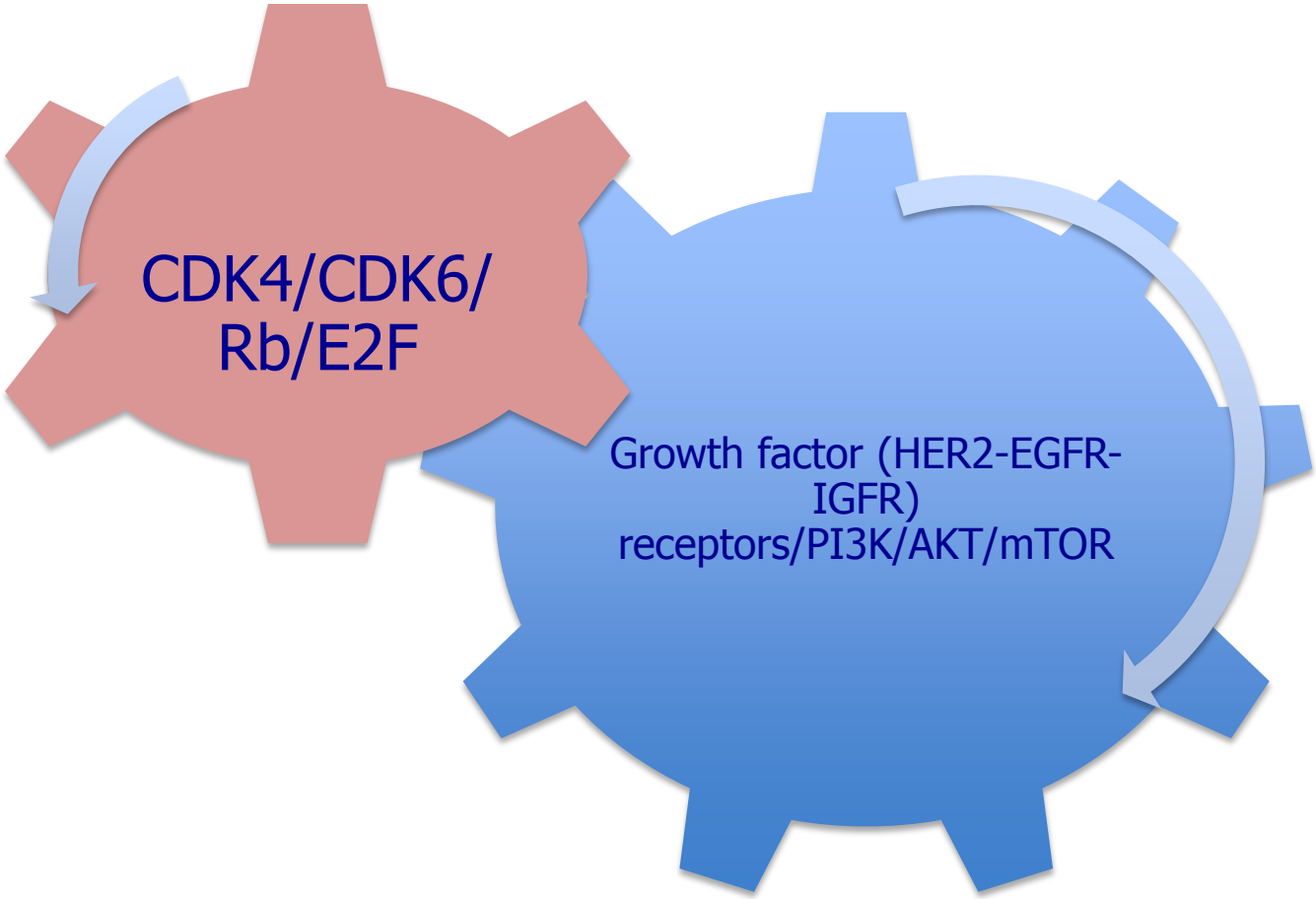
Endocrine resistance

- endocrine therapy is often regarded as a prototype of biologically targeted treatment.

- by contrast with HER2-overexpressing disease, **pathway-directed breakthrough innovations have been rare in this subtype.**

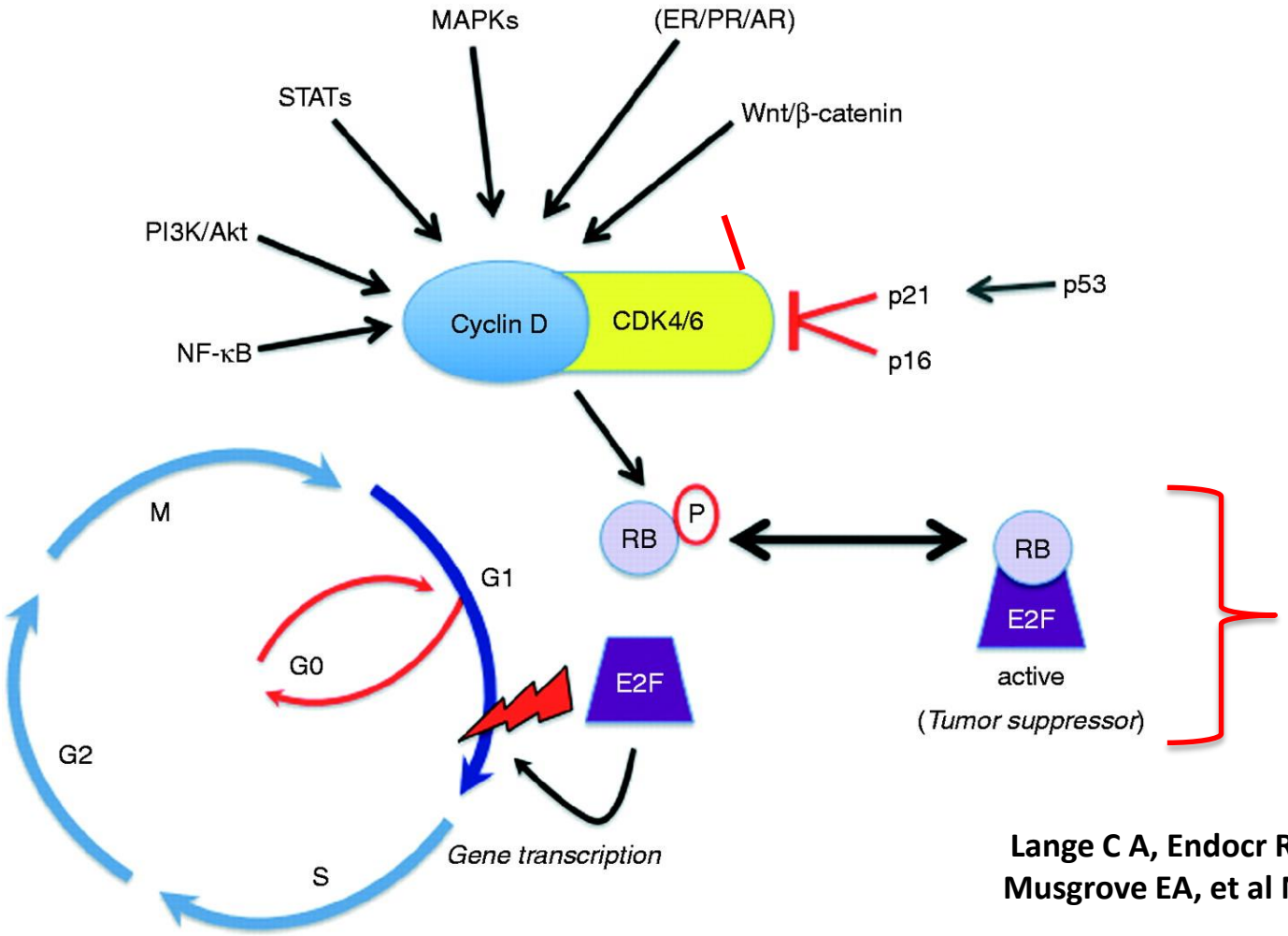
- in the advanced disease setting, with every further line of palliative endocrine therapy, shorter durations of progression-free survival are seen.

Two major axes in endocrine resistance



Shift from oestrogen-dependent tumor growth to the activation of alternate growth factor signalling pathways in the absence of oestrogen

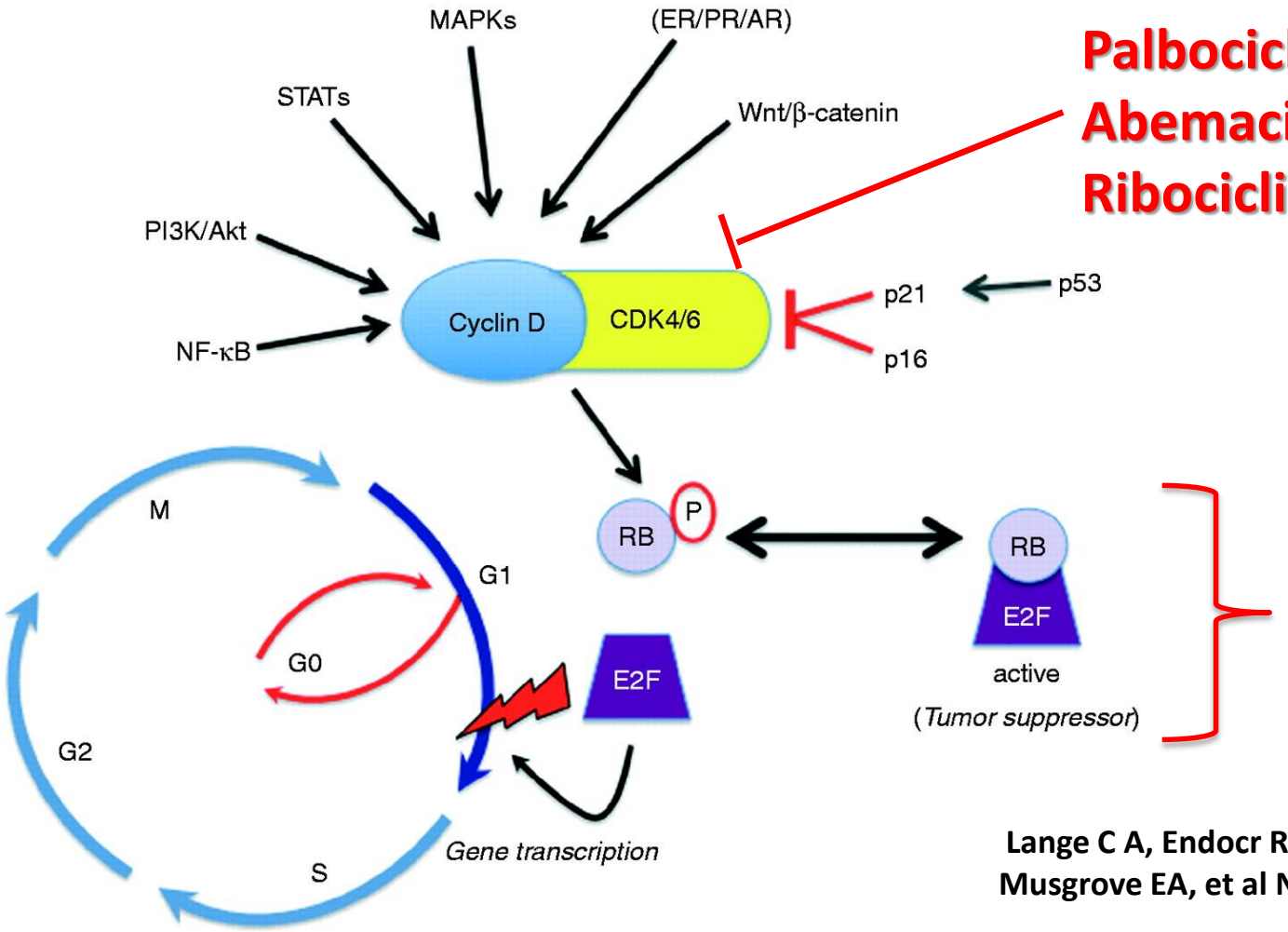
CDK4/6



Lange C A, Endocr Relat Cancer 2011
Musgrove EA, et al Nat Rev Can 2011

pRb phosphorylation and inactivation

CDK4/6 inhibitors



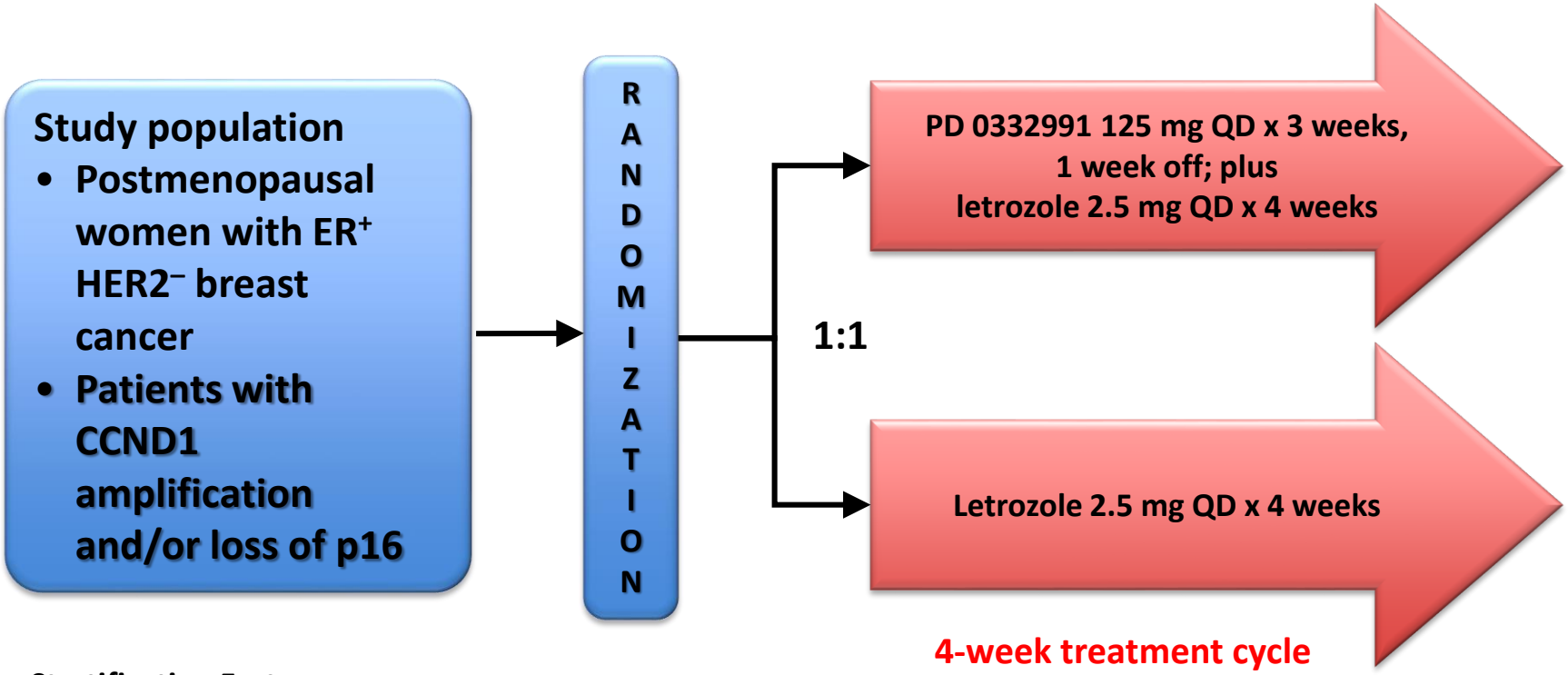
Lange C A, Endocr Relat Cancer 2011
Musgrove EA, et al Nat Rev Can 2011

Block of pRb phosphorylation

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 Slamon

Study Design



Stratification Factors

- Disease site (visceral vs bone only vs other)
- Disease-free interval (>12 vs ≤12 mo from end of adjuvant to recurrence or de novo advanced disease)

Finn RS, et al ASCO 2013

Two cohorts
(sequential accrual: two-part study design)

- **Cohort 1 (exploratory analysis)**
  - HR pos
  - HER-2 neg

- **Cohort 2 (PFS, primary end-point)**
  - HR pos
  - HER-2 neg
  - Ampl. cyclin D1
  - Loss p16
  - Both

Initial statistical design: one-side α of 0.10 with 80% power to detect an HR 0.67 (PFS 9 m vs 13.5m) → 150 pts

i. Cohort 2 stopped after unplanned interim analysis of cohort 1
ii. Primary endopoint (PFS) amended for combined analysis
iii. Cohort 2: 150 total pts → Cohort 1 + 2: **165 (66 + 99)**

Lancet Oncol 2015

	Both cohorts		Cohort 1		Cohort 2	
	Palbociclib plus letrozole (n=84)	Letrozole (n=81)	Palbociclib plus letrozole (n=34)	Letrozole (n=32)	Palbociclib plus letrozole (n=50)	Letrozole (n=49)
Median age (years)	63 (54–71)	64 (56–70)	66 (56–72)	64 (57–70)	62 (54–70)	63 (56–71)
ECOG performance status						
0	46 (55%)	45 (56%)	23 (68%)	20 (63%)	23 (46%)	25 (51%)
1	38 (45%)	36 (44%)	11 (32%)	12 (38%)	27 (54%)	24 (49%)
Disease stage						
III	2 (2%)	1 (1%)	2 (6%)	0	0	1 (2%)
IV	82 (98%)	80 (99%)	32 (94%)	32 (100%)	50 (100%)	48 (98%)
Disease site*						
Visceral	37 (44%)	43 (53%)	10 (29%)	11 (34%)	27 (54%)	32 (65%)
Bone only	17 (20%)	12 (15%)	7 (21%)	6 (19%)	10 (20%)	6 (12%)
Other (non-visceral)	30 (36%)	26 (32%)	17 (50%)	15 (47%)	13 (26%)	11 (23%)
Disease-free interval*						
>12 months from adjuvant treatment to recurrence	25 (30%)	30 (37%)	10 (29%)	10 (31%)	15 (30%)	20 (41%)
≤12 months from adjuvant treatment to recurrence or de-novo advanced disease	59 (70%)	51 (63%)	24 (71%)	22 (69%)	35 (70%)	29 (59%)
De-novo advanced disease only	44 (52%)	37 (46%)	19 (56%)	17 (53%)	25 (50%)	20 (41%)
Previous systemic treatment						
None	44 (52%)	37 (46%)	19 (56%)	17 (53%)	25 (50%)	20 (41%)
Chemotherapy	34 (40%)	37 (46%)	11 (32%)	14 (44%)	23 (46%)	23 (47%)
Hormonal	27 (32%)	28 (35%)	11 (32%)	11 (34%)	16 (32%)	17 (35%)
Tamoxifen	24 (29%)	24 (30%)	8 (24%)	8 (25%)	16 (32%)	16 (33%)
Anastrozole	8 (10%)	11 (14%)	4 (12%)	5 (16%)	4 (8%)	6 (12%)
Letrozole	2 (2%)	1 (1%)	0	0	2 (4%)	1 (2%)
Exemestane	4 (5%)	2 (2%)	3 (9%)	1 (3%)	1 (2%)	1 (2%)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group. *Based on case report form data.

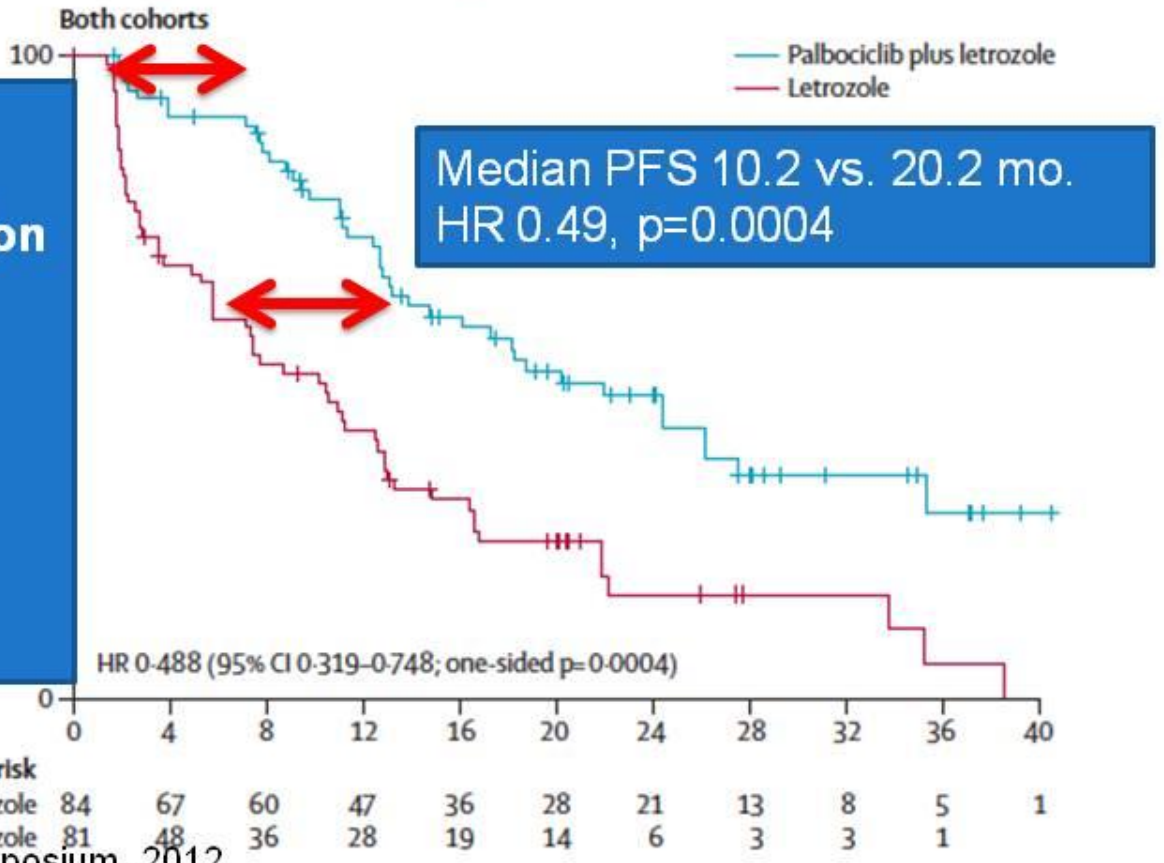
17%

Table 1: **Baseline characteristics (intention-to-treat population)**

PFS: both cohorts

PALOMA-1: Randomized open-label phase II trial

- **FDA Breakthrough Designation**
  - **April, 2013**
- **Accelerated FDA approval**
  - **February 3, 2015**

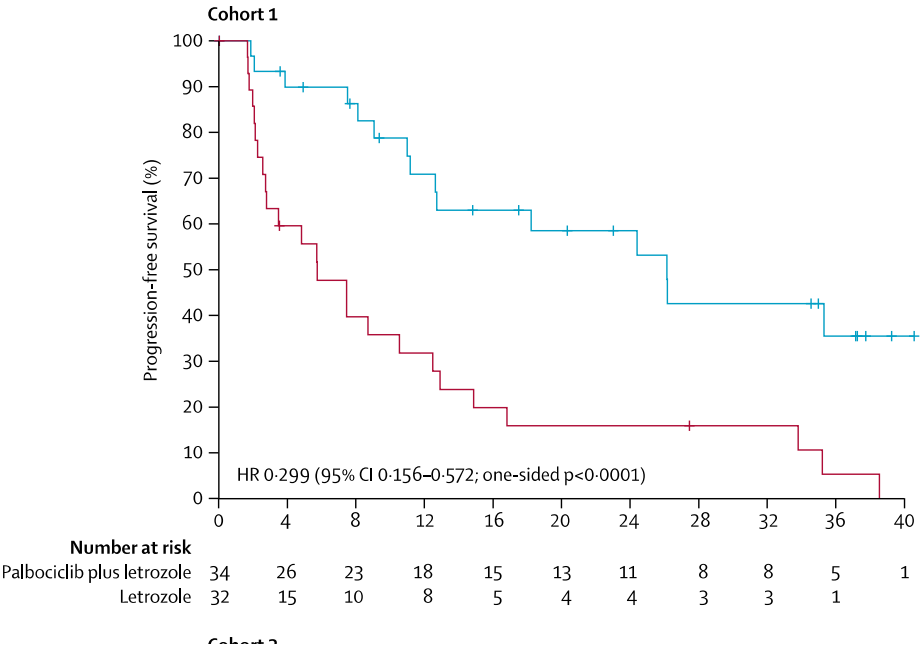


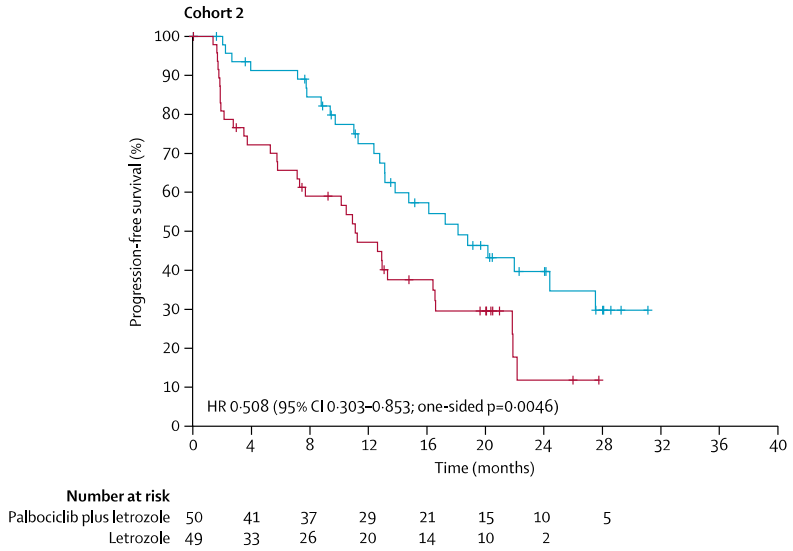
Finn et al. San Antonio Breast Cancer Symposium, 2012
Finn et al. AACR, 2014; Finn et al. Lancet Oncol, 2015

PRESENTED AT: ASCO Annual '15 Meeting

Presented By Joseph Sparano at 2015 ASCO Annual Meeting

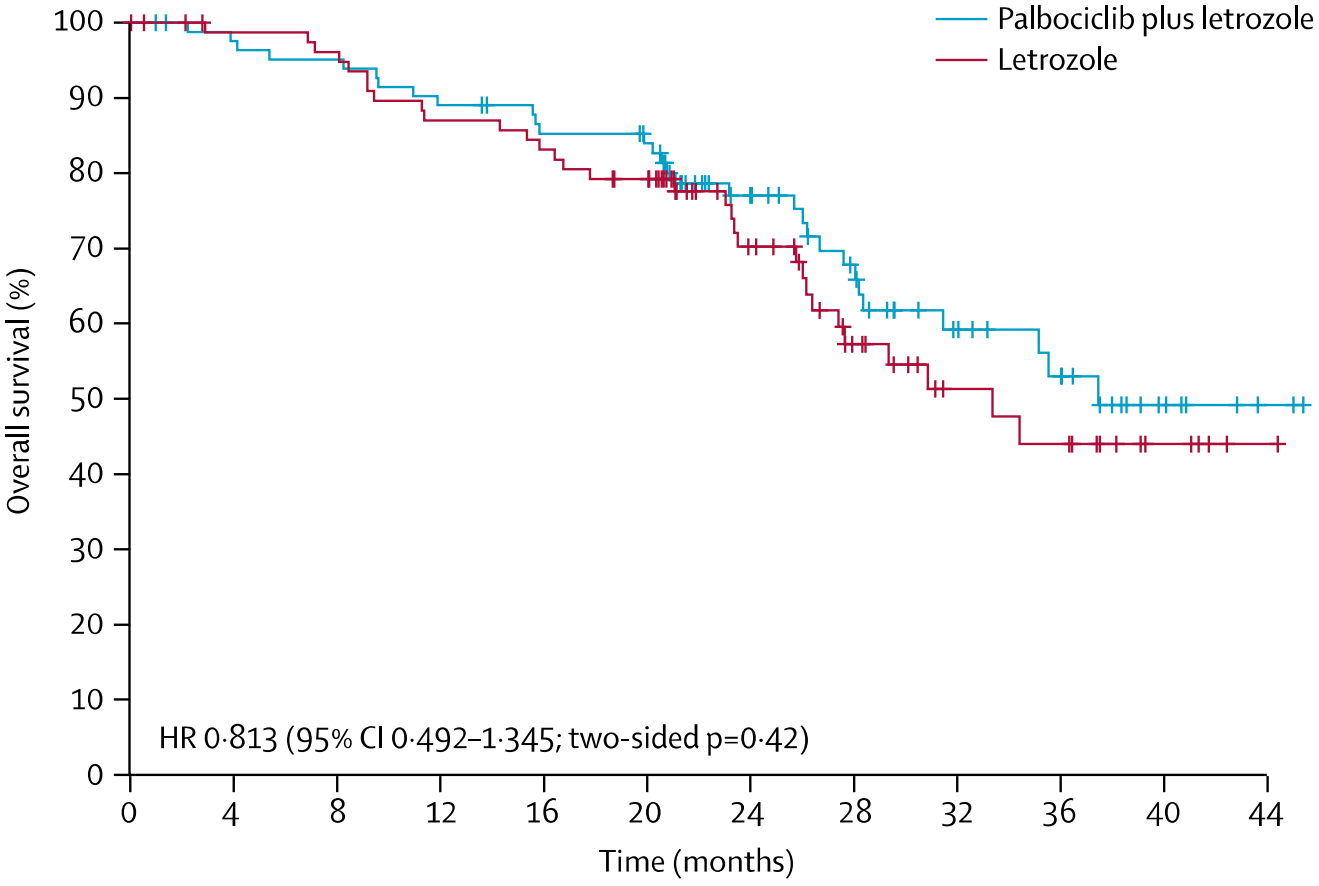
PFS: cohort 1 and cohort2





Lancet Oncol 2015

OS



Number at risk												
Palbociclib plus letrozole	84	80	78	73	68	65	47	35	22	17	7	2
Letrozole	81	76	74	67	64	59	37	23	14	12	5	1

Lancet Oncol 2015

	Palbociclib plus letrozole (n=83)			Letrozole (n=77)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any adverse event	19 (23%)	49 (59%)	14 (17%)	49 (64%)	16 (21%)	0
Neutropenia	17 (20%)	40 (48%)	5 (6%)	3 (4%)	1 (1%)	0
Leucopenia	20 (24%)	16 (19%)	0	2 (3%)	0	0
Fatigue	30 (36%)	2 (2%)	2 (2%)	17 (22%)	1 (1%)	0
Anaemia	24 (29%)	4 (5%)	1 (1%)	4 (5%)	1 (1%)	0
Nausea	19 (23%)	2 (2%)	0	9 (12%)	1 (1%)	0
Arthralgia	18 (22%)	1 (1%)	0	10 (13%)	2 (3%)	0
Alopecia	18 (22%)	NA	NA	2 (3%)	NA	NA
Diarrhoea	14 (17%)	3 (4%)	0	8 (10%)	0	0
Hot flush	17 (21%)	0	NA	9 (12%)	0	NA
Thrombocytopenia	12 (14%)	2 (2%)	0	1 (1%)	0	0
Decreased appetite	12 (14%)	1 (1%)	0	5 (6%)	0	0
Dyspnoea	11 (13%)	2 (2%)	0	5 (6%)	1 (1%)	0
Nasopharyngitis	13 (16%)	0	0	8 (10%)	0	0
Back pain	11 (13%)	0	1 (1%)	11 (14%)	1 (1%)	0
Headache	12 (14%)	0	0	8 (10%)	0	0
Vomiting	12 (14%)	0	0	2 (3%)	1 (1%)	0
Asthenia	9 (11%)	2 (2%)	0	3 (4%)	0	0
Bone pain	8 (10%)	1 (1%)	1 (1%)	3 (4%)	0	0
Constipation	10 (12%)	0	0	7 (9%)	0	0
Cough	10 (12%)	0	0	8 (10%)	0	0
Stomatitis	10 (12%)	0	0	2 (3%)	0	0
Epistaxis	9 (11%)	0	0	1 (1%)	0	0
Influenza	8 (10%)	1 (1%)	0	1 (1%)	0	0
Musculoskeletal pain	8 (10%)	1 (1%)	0	5 (6%)	0	0
Upper respiratory tract infection	8 (10%)	1 (1%)	0	2 (3%)	0	0
Dizziness	8 (10%)	0	0	3 (4%)	0	0
Peripheral neuropathy	8 (10%)	0	0	4 (5%)	0	0
Oropharyngeal pain	8 (10%)	0	0	1 (1%)	0	0
Pain in extremity	8 (10%)	0	0	6 (8%)	0	0

Dose modifications

	Dose interruption	Dose reduction	Study discontinuation
ARM A	33%	40%	13%
ARM B	4%	-	2%

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*

PALOMA3 Study Design

- HR+, HER2– ABC
- Pre-/peri-* or post-menopausal
- Progressed on prior endocrine therapy:
  - On or within 12 mo adjuvant
  - On therapy for ABC
- ≤1 prior chemotherapy regimen for advanced cancer

*All received goserelin.

2:1 Randomization

N=521

Stratification:

- Visceral metastases
- Sensitivity to prior hormonal therapy
- Pre-/peri- vs Post-menopausal

n=347 → **Palbociclib (125 mg QD; 3 wks on/1 wk off) + Fulvestrant† (500 mg IM q4w)**

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

- ***Post-menopausal patients must have progressed on prior aromatase inhibitor therapy.***

†administered on Days 1 and 15 of Cycle 1.

Clinicaltrials.gov NCT01942135

Paloma-3

- Primary end-point: PFS (ITT)

➢ 6.0 months → 9.38 months (HR 0.64, a=0.025)

➢ Interim analysis (cut-off date: 05 dec 2014) after 195 PFS events (NEJM 2005)

➢ Final analysis (cut-off date: 16 mar 2015) after 259 PFS events (Lancet Oncol 2016)

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

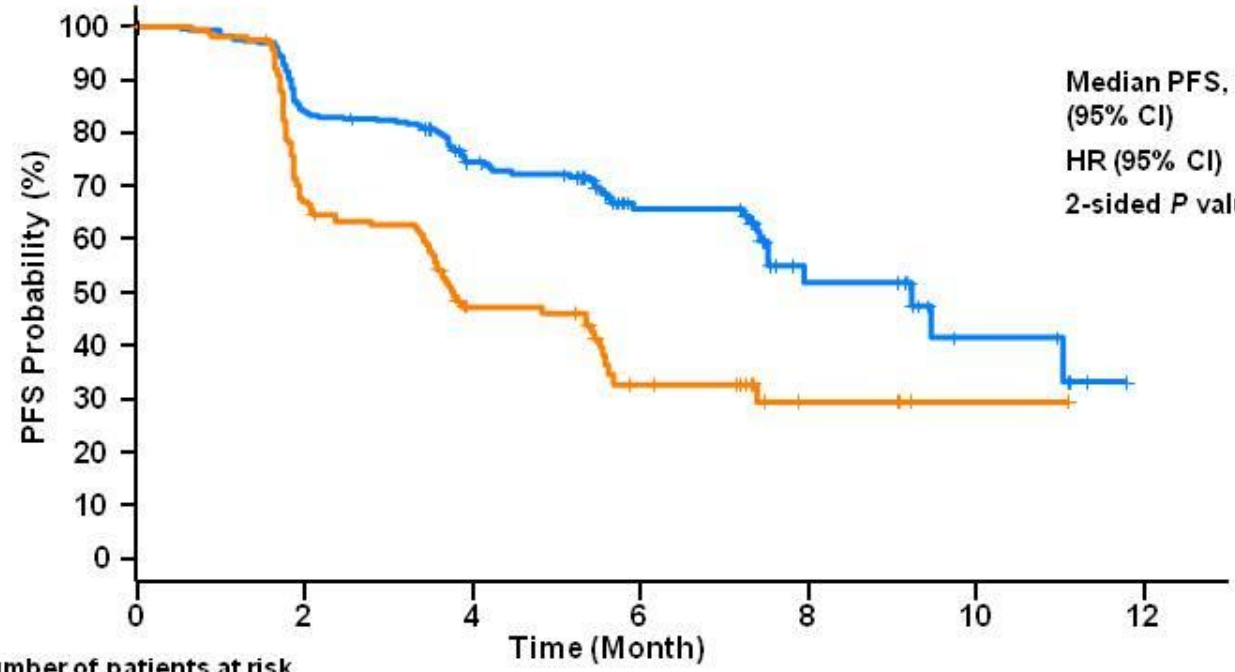
[a]Based on randomization; [b]lung, liver, brain, pleural, and peritoneal involvement.

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.

Primary Endpoint: PFS (ITT Population)



	Palbociclib + Fulvestrant n=347	Placebo + Fulvestrant n=174
Median PFS, months (95% CI)	9.2 (7.5, NE)	3.8 (3.5, 5.5)
HR (95% CI)	0.422 (0.318, 0.560)	
2-sided *P* value	<0.000001	

Number of patients at risk

PAL+FUL	347	279	132	59	16	6
PCB+FUL	174	109	42	16	6	1

CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; NE=not estimable; PFS=progression-free survival.

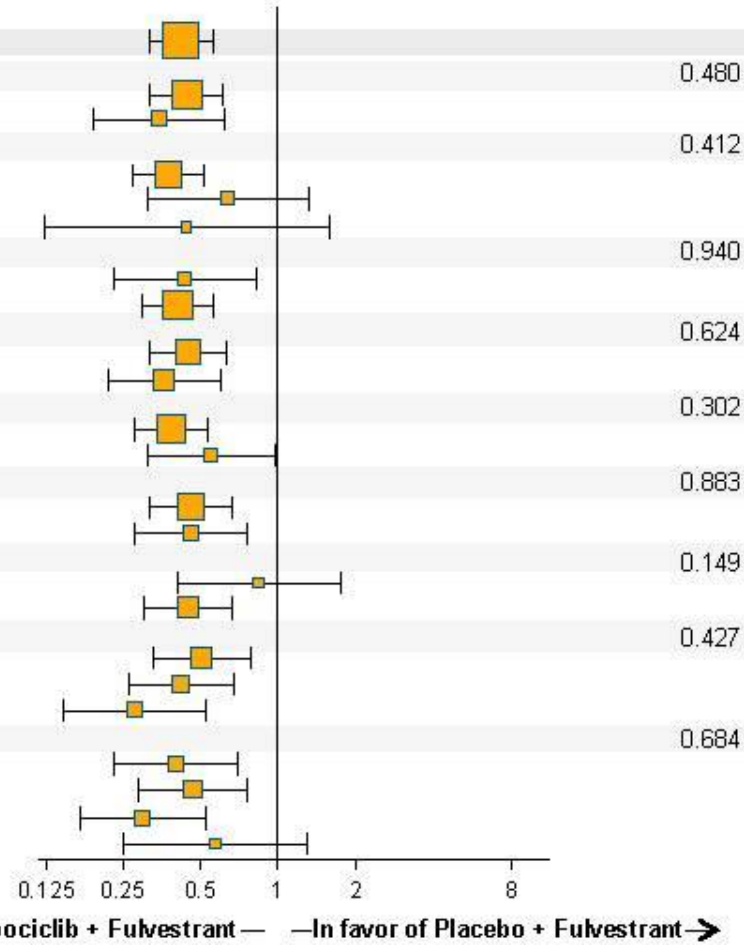
Preplanned interim analysis

Presented By Nicholas Turner at 2015 ASCO Annual Meeting

NEJM 2015

PFS: Patient Subgroup Analysis

Subgroup	n (%)	*P* value for Interaction
All randomized patients (ITT)	521 (100)	
Age		0.480
<65 Years	392 (75.2)	
≥65 Years	129 (24.8)	
Race[a]		0.412
White	385 (73.9)	
Asian	105 (20.2)	
Black and other	29 (5.6)	
Menopausal status at study entry		0.940
Pre/Peri	108 (20.7)	
Post	413 (79.3)	
Site of metastatic disease		0.624
Visceral	311 (59.7)	
Non visceral	210 (40.3)	
Sensitivity to prior hormonal therapy		0.302
Yes	410 (78.7)	
No	111 (21.3)	
Receptor status		0.883
ER+/PgR+	349 (67.0)	
ER+/PgR-	139 (26.7)	
Disease-free interval		0.149
≤24 months	65 (12.5)	
>24 months	281(53.9)	
Prior chemotherapy		0.427
(Neo) adjuvant only	219 (42.0)	
Metastatic +/- (neo)adjuvant	170 (32.6)	
No prior chemotherapy	132 (25.3)	
Prior lines of therapy in advanced setting		0.684
0	129 (24.8)	
1	202 (38.8)	
2	133 (25.5)	
3+	57 (10.9)	



ER=estrogen receptor; PgR=progesterone receptor.
[a]Race was unspecified in 2 patients (1 in each treatment group).

Summary of Key Secondary Efficacy Endpoints

	Palbociclib + Fulvestrant (n=347), % of patients	Placebo + Fulvestrant (n=174), % of patients	*P* value
ORR	10.4	6.3	0.1582
CBR*	34.0	19.0	0.0004

*** CBR is underestimated.**

36% of palbociclib and 24% of placebo pts remain on study treatment with <24 weeks of follow up.

At the time of the interim analysis, OS data was immature with 28 deaths.

CBR=clinical benefit rate (CR+PR+SD ≥24 wk); CR=complete response; ORR=objective response (CR+PR); OS=overall survival; PR=partial response; SD=stable disease.

Adverse Events—All Cause

AE, %	Palbociclib + Fulvestrant (n=345)			Placebo + Fulvestrant (n=172)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any AE	98	59	11	89	16	2
Neutropenia	79	53	9	3	0	1
Leukopenia	46	25	1	4	0	1
Anemia	26	3	0	10	2	0
Thrombocytopenia	19	2	1	0	0	0
Fatigue	38	2	0	27	1	0
Nausea	29	0	0	26	1	0
Headache	21	<1	0	17	0	0
Upper respiratory infection[a]	19	<1	0	16	0	0
Diarrhea	19	0	0	17	1	0
Constipation	17	0	0	14	0	0
Alopecia	15	0	0	6	0	0

AE=adverse event. AEs with ≥15% incidence in the palbociclib + fulvestrant group reported.

[a]Upper respiratory infection includes influenza, influenza-like illness, laryngitis, nasopharyngitis or pharyngitis, rhinitis, sinusitis, and upper respiratory tract infection.

Treatment Summary

Treatment Summary (AT population)	Palbociclib + Fulvestrant (n=345)	Placebo + Fulvestrant (n=172)
Relative fulvestrant dose intensity (%), median	99.7	100
Relative palbociclib/placebo dose intensity (%), median	91.7	100
Dose interruptions due to AEs, %	54	4
Cycle delays due to AEs, %	22	1
Dose reductions due to AEs, %	32	2
Discontinuations due to AEs, %*	**2.6**	**1.7**

- **Neutropenia was the most common AE leading to dose reductions (21%) and interruptions (45%)**

*ITT population.
AE=adverse event; AT=as treated.

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

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PALOMA-3: PFS in Overall Population and Specific Subgroups: PI3K status and HR expression level

Final analysis; Median follow-up: 8.9 mos

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

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

Lancet Oncol 2016

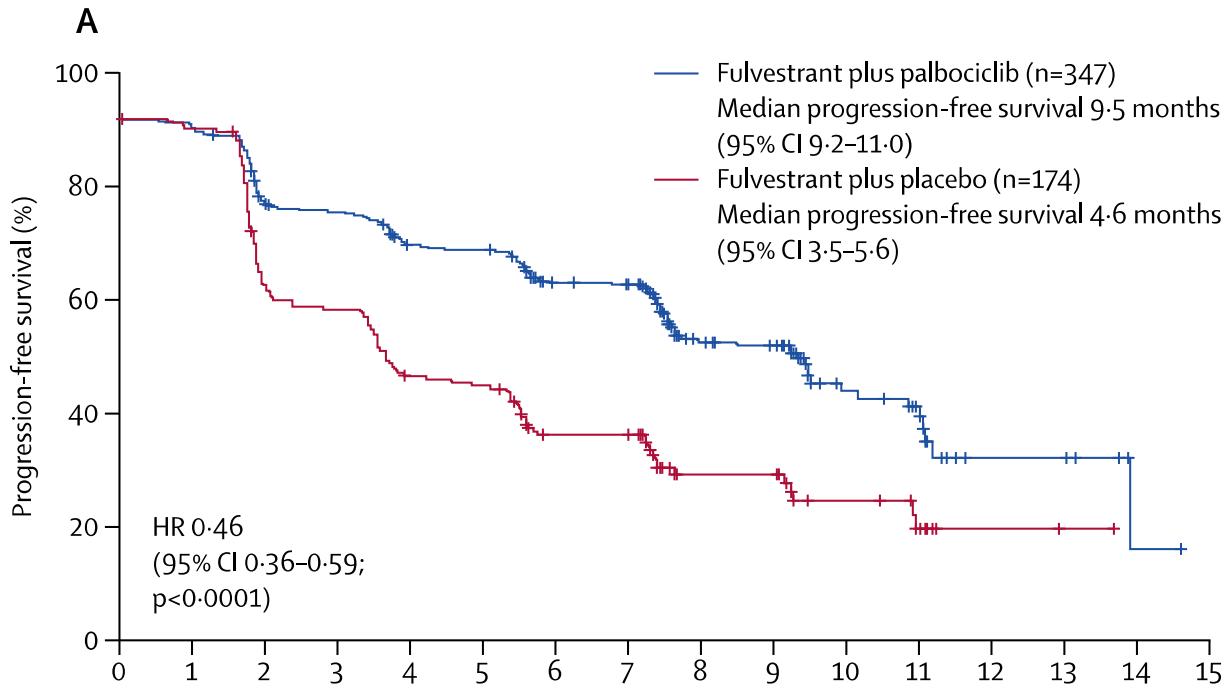
PALOMA-3
Response and Clinical Benefit Rates: final analysis

Median follow-up: 8.9 mos

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

Lancet Oncol 2016

PFS: ITT population final analysis



Number at risk																
Fulvestrant plus palbociclib	347	333	281	273	247	244	202	197	91	85	32	23	7	7	1	0
Fulvestrant plus placebo	174	165	112	105	83	80	59	58	22	22	13	7	2	1	0	0

Lancet Oncol 2016

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

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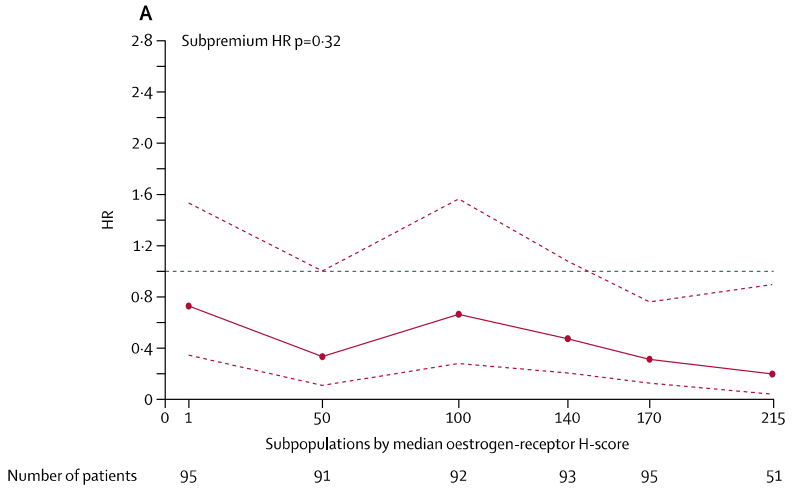
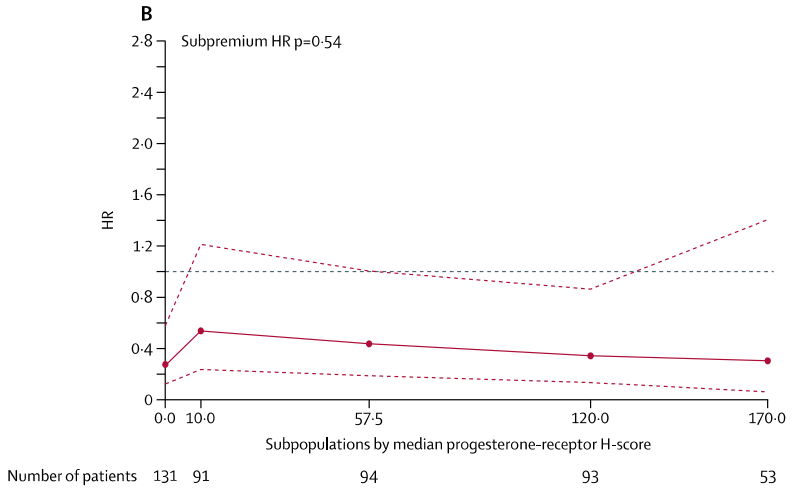
STEPP analysis for ER pos



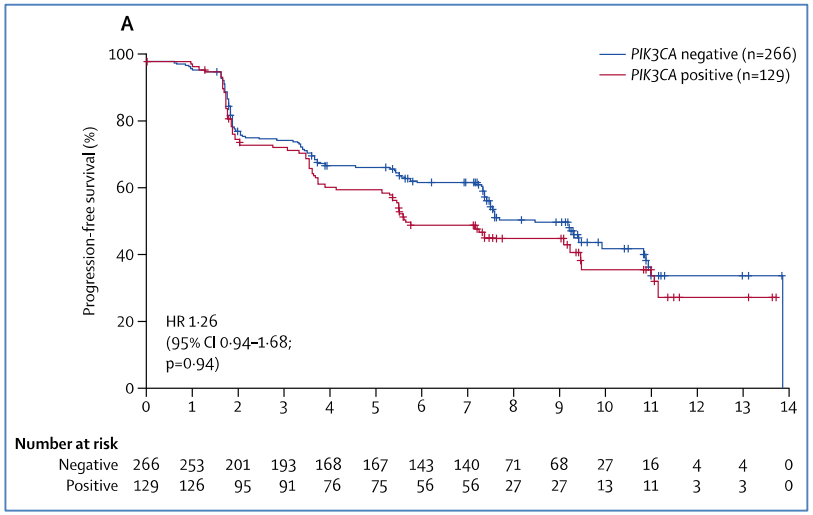
STEPP analysis for PgR pos



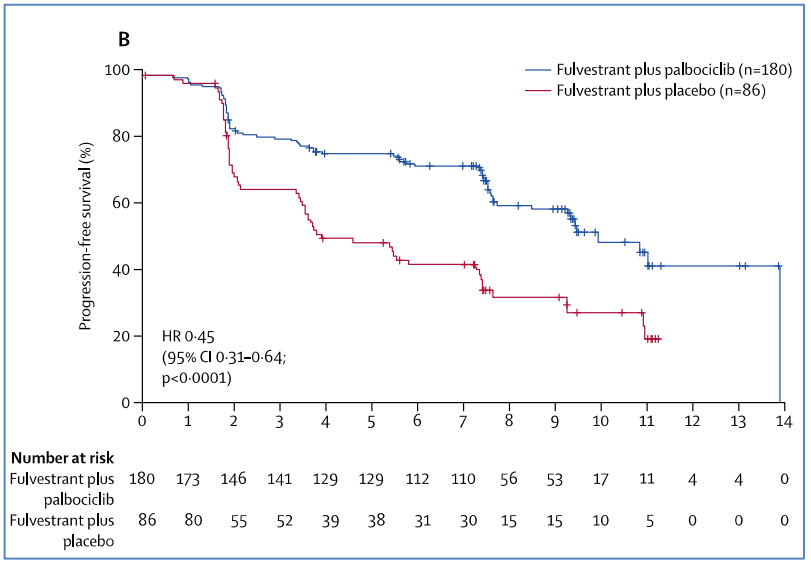
efficacy of fulvestrant plus palbociclib were not significantly associated with expression level of oestrogen or progesteron receptors

Lancet Oncol 2016

PI3K status

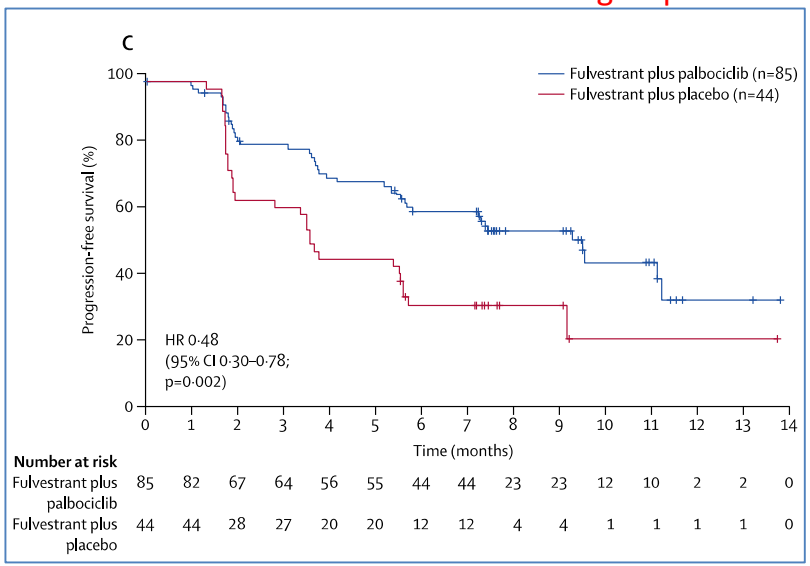


patients with PIK3CA mutations and patients without mutations irrespective of treatment assignment



patients without PIK3CA mutations in the palbociclib and control groups

patients with PIK3CA mutations in the palbociclib and control groups



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PALOMA-3: Conclusions

The significant improvement in efficacy with the addition of palbociclib to fulvestrant was maintained **through longer follow-up**

- Benefit demonstrated across all subgroups

No new safety concerns were identified; certain hematologic AEs were more common with palbociclib than fulvestrant alone

- The incidence of febrile neutropenia was similar for both treatment arms (0.9% vs 0.6%, respectively)
- Discontinuations due to AEs were similar with palbociclib + fulvestrant and placebo + fulvestrant (4% vs 2%, respectively)

The benefits of the combination **are maintained irrespective of** expression level of hormone receptors and PI3K status

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

Open Questions

- genetic changes in cyclin D1 and p16 are known to occur in breast cancer and might have a role in the further selection of patients for treatment with a CDK4/6 inhibitor.

- **however, in clinical trials, patients selection on the basis of cyclin D1 amplification, p16 loss or PI3K status was not associated with an improved outcome from palpociclib**

- one of the most important markers of sensitivity to palbociclib is the presence of an intact Rb pathway; however, since pRb loss is uncommon in oestrogen receptor-positive, HER2-negative breast cancers, it was not used as a prospective independent biomarker for patient selection in the present study.

oestrogen receptor positivity is currently the best and most effective predictive marker for the identification of patients likely to respond to CDK4/6 inhibition.