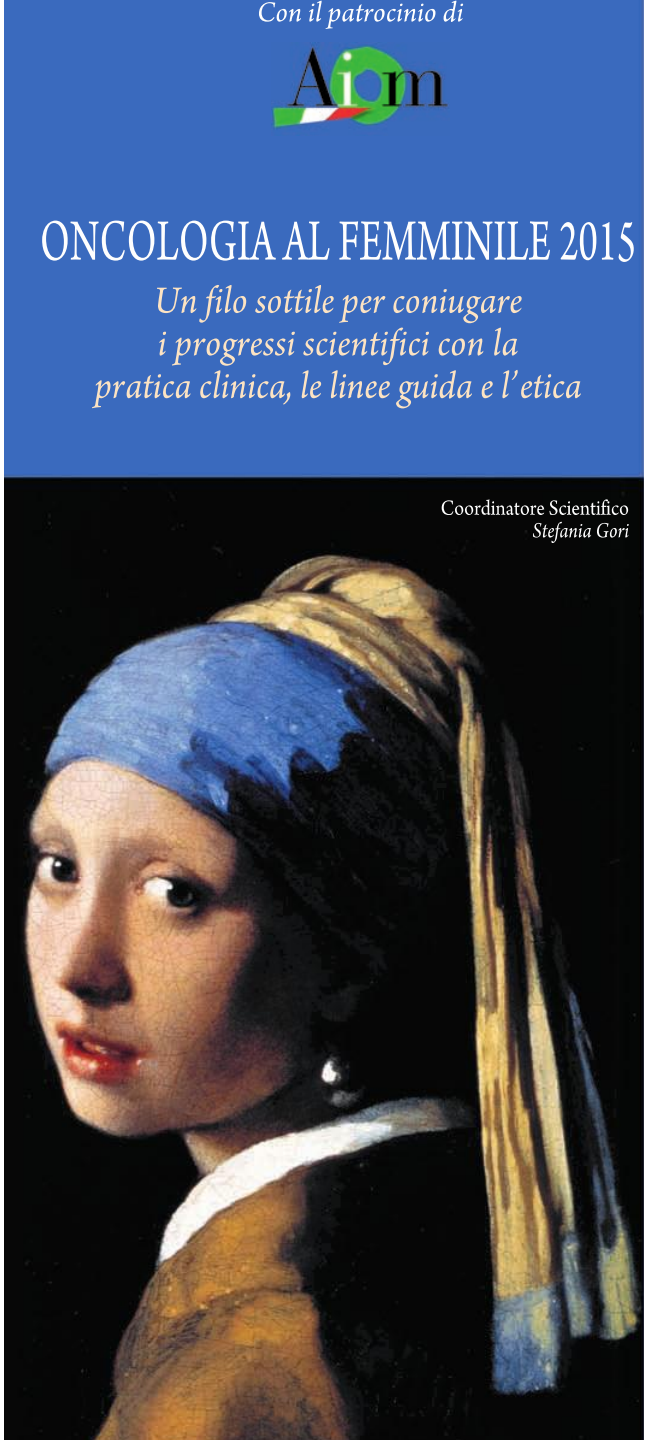


Gli inibitori di CDK4/6 nel carcinoma mammario metastatico

Laura Orlando
UOC Oncologia & Breast Unit
Brindisi

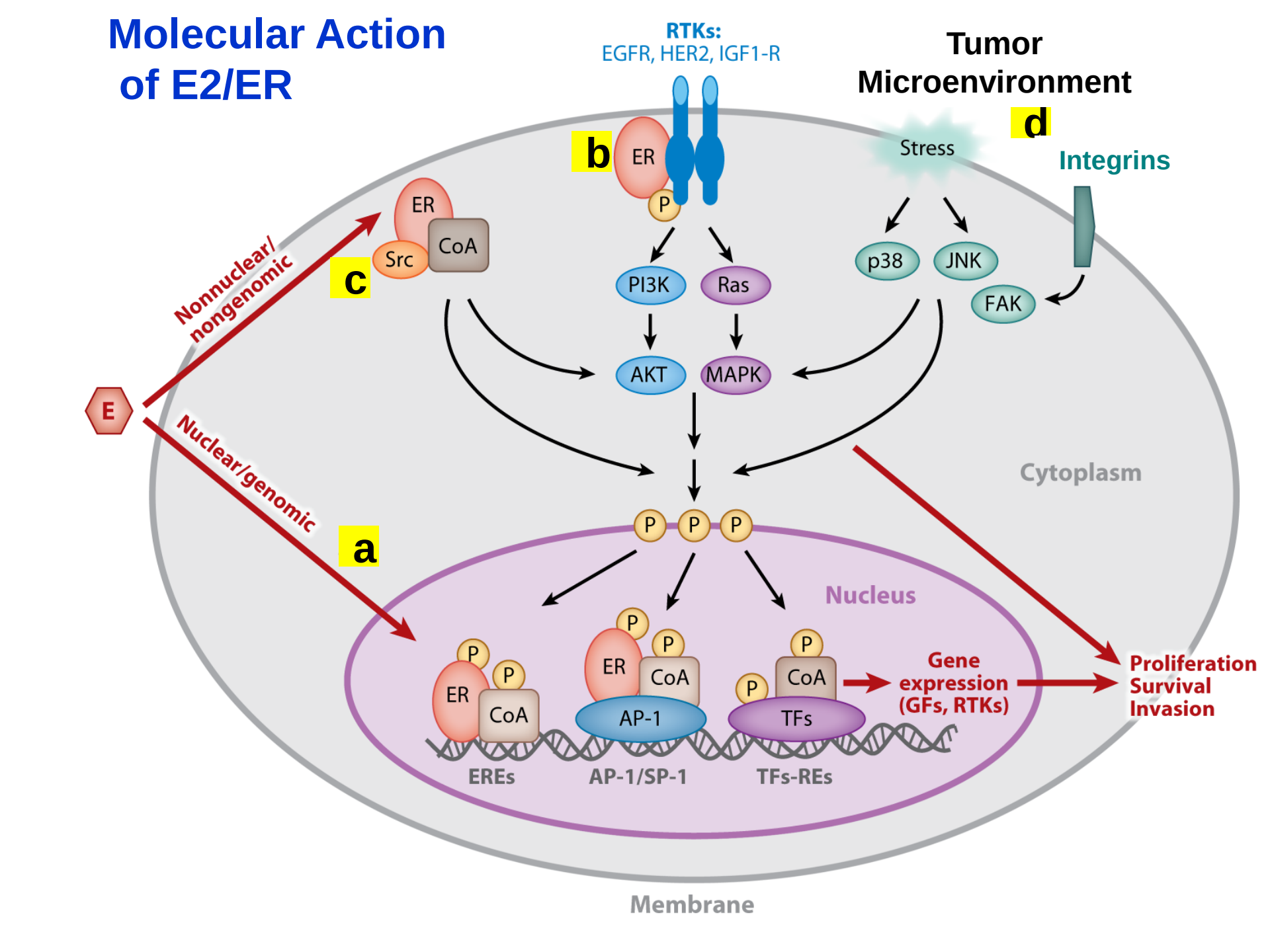
Verona 19/09/2015

OUTLINE

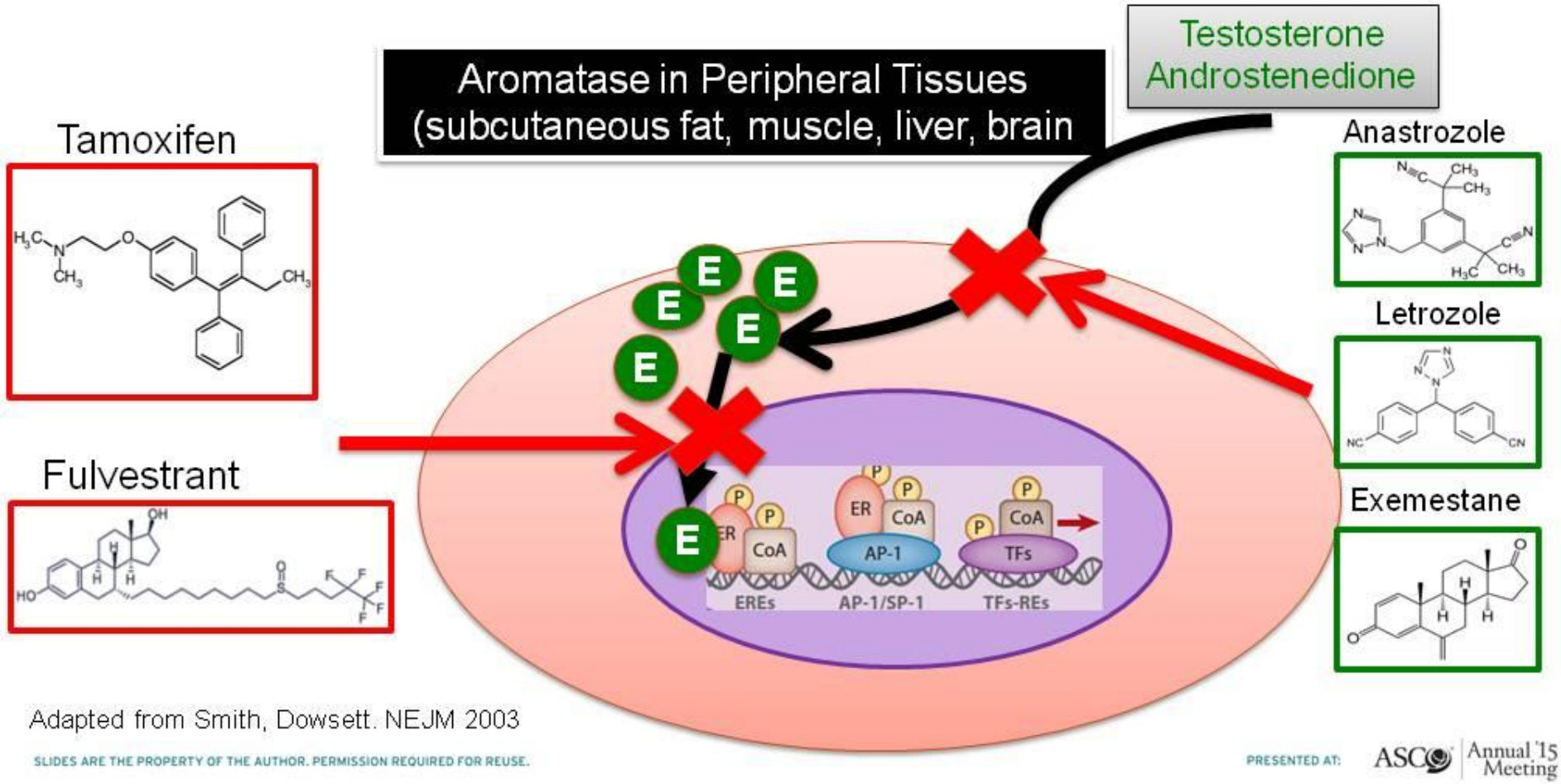
- Anti CDK4/CDK6 nel tumore HR+

- Anti CDK4/CDK6 nel tumore HER+

- Anti CDK4/CDK6 nel tumore TN


Molecular Action of E2/ER
RTKs:
EGFR, HER2, IGF1-R
Tumor Microenvironment
d
Stress
Integrins
b
ER
P
c
ER
Src
CoA
Nonnuclear/ nongenomic
E
Nuclear/genomic
a
PI3K
Ras
p38
JNK
FAK
AKT
MAPK
Cytoplasm
P
Nucleus
ER
CoA
AP-1
TFs
Gene expression (GFs, RTKs)
Proliferation
Survival
Invasion
EREs
AP-1/SP-1
TFs-REs
Membrane

Antiestrogen Therapy: Aromatase Inhibitors vs. Tamoxifen & Fulvestrant



Adapted from Smith, Dowsett. NEJM 2003

Presented By Joseph Sparano at 2015 ASCO Annual Meeting

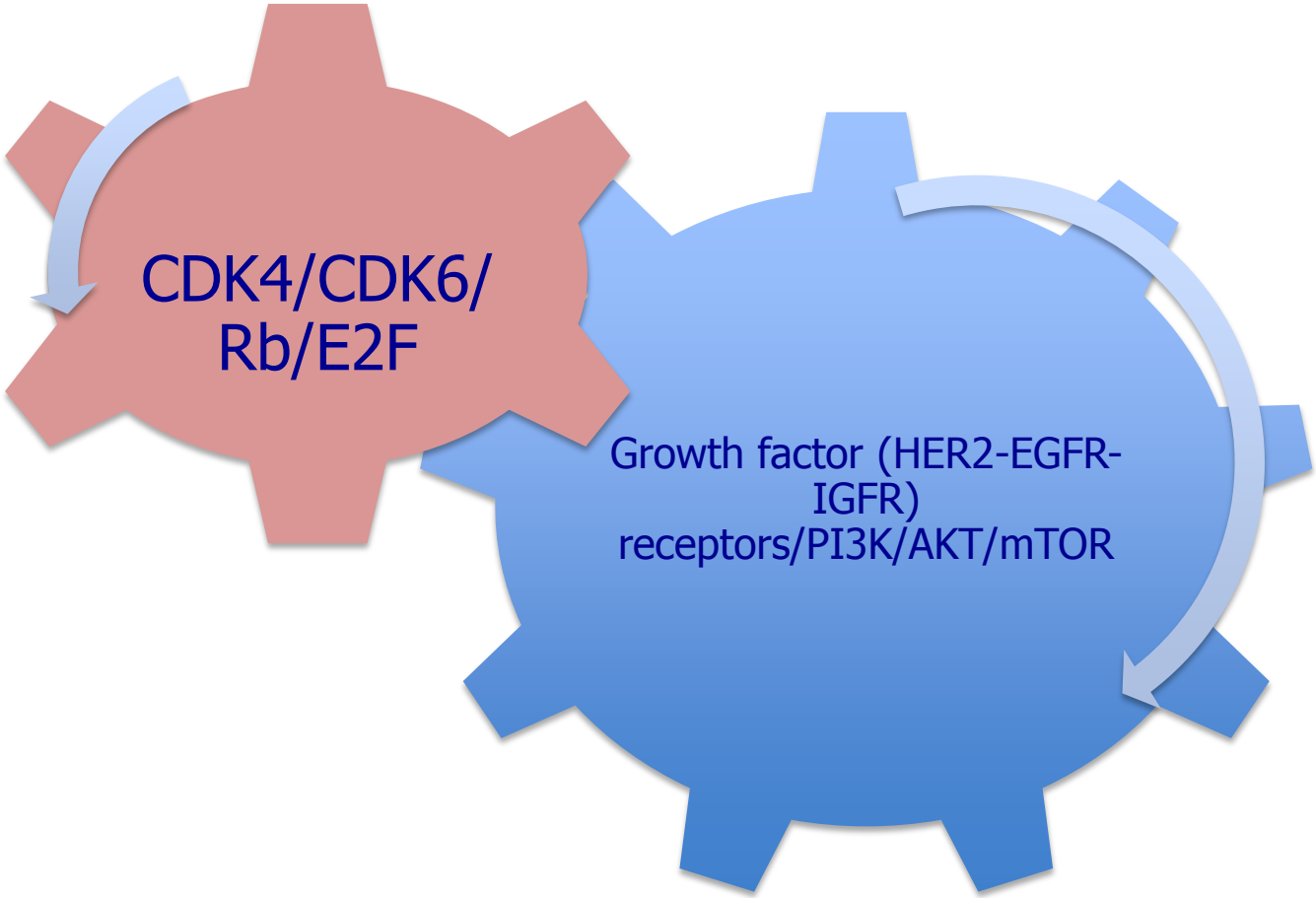
Endocrine resistance

- 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.**

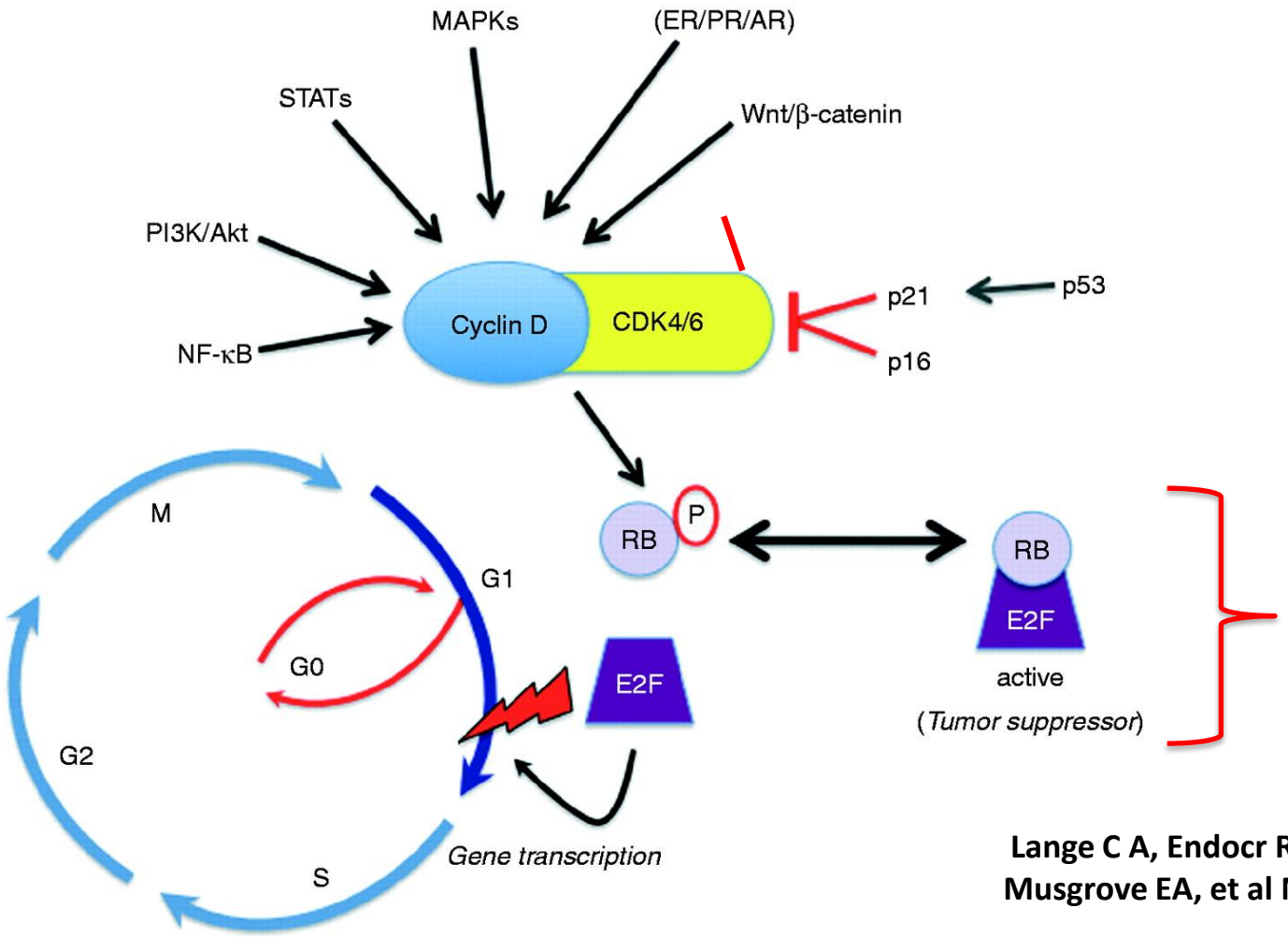
- in the advanced disease setting, with every further line of palliative endocrine therapy, shorter durations of progression-free survival are seen.

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

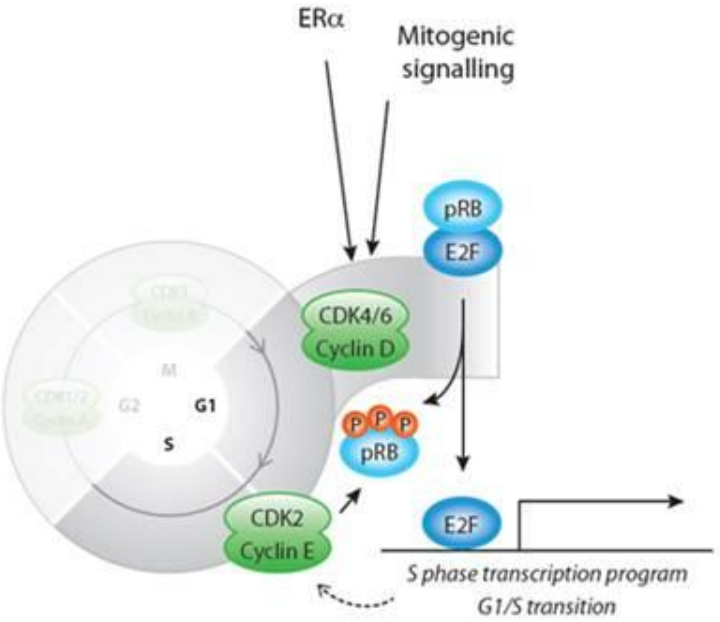


Lange C A, Endocr Relat Cancer 2011
Musgrove EA, et al Nat Rev Can 2011

pRb phosphorylation and inactivation

CDK4/6 in Breast Cancer

- **Resistance to endocrine therapy presents a major clinical challenge.**
- **The growth of HR+ breast cancer is dependent on Cyclin D1, a direct transcriptional target of ER.**
- **Cyclin D1 activates CDK 4/6 resulting in G1–S phase transition and entry into the cell cycle.[1]**
- **Cell line models of endocrine resistance remain dependent on Cyclin D1 and CDK4/6.[2,3]**



CDK=cyclin-dependent kinase; ER=estrogen receptor; HR+=hormone receptor-positive.

1. Asghar U, et al. *Nat Rev Drug Discov*. 2015;14:130-46.
2. Miller T, et al. *Cancer Discov*. 2011; 1:338-51.
3. Thangavel C, et al. *Endocr Relat Cancer*. 2011;18:333-45.

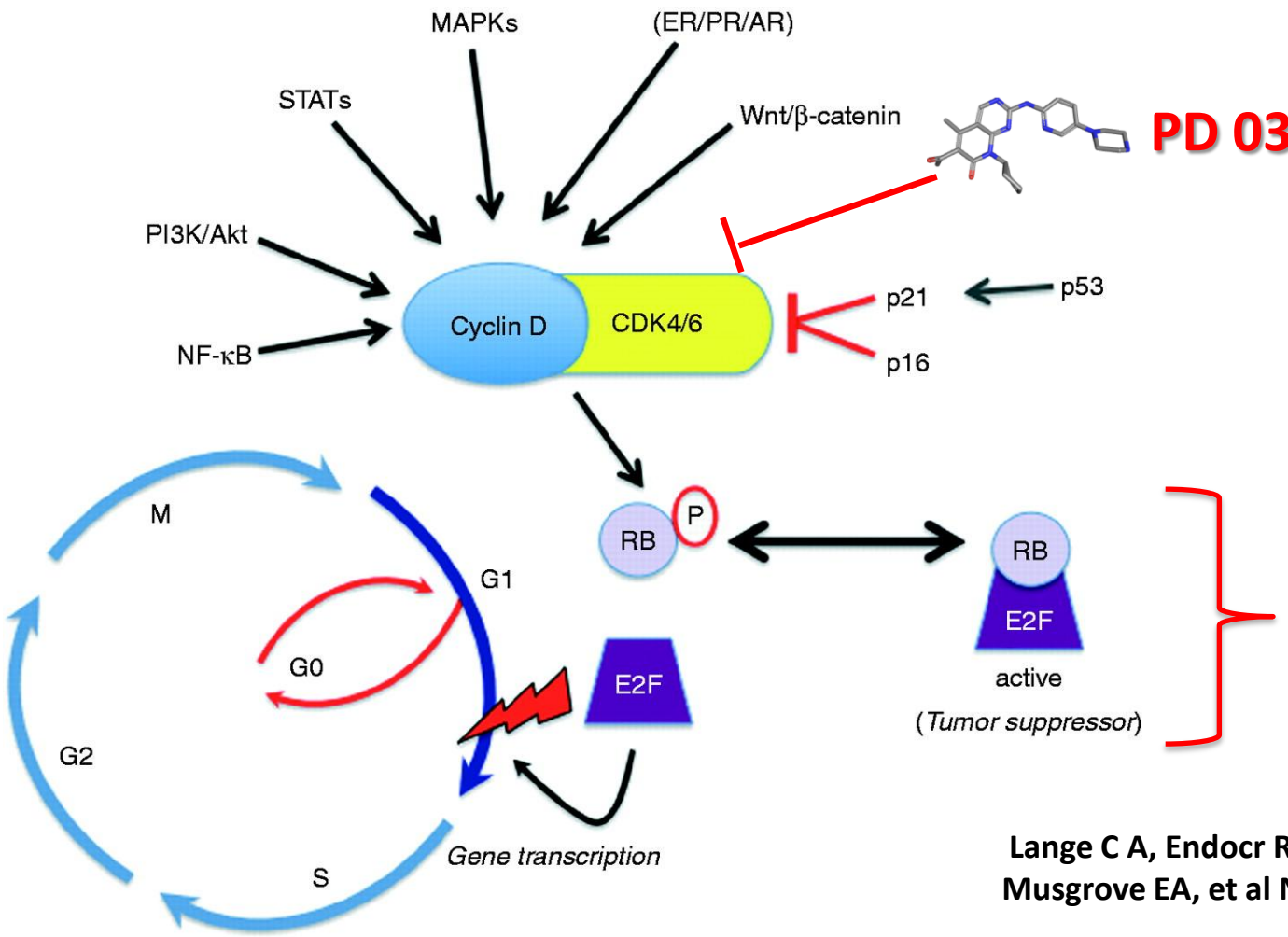
Palbociclib

- is an orally active selective inhibitor of CDK4/6 that inhibits cell proliferation and DNA synthesis by preventing cell-cycle progression from G1 to S phase [1]

- is active in cell line models of endocrine therapy resistance[2]

1. Toogood J Med Chem 2005
2. Finn Breast Cancer Res 2009

PD 0332991 and CDK4/6



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

Block of pRb phosphorylation

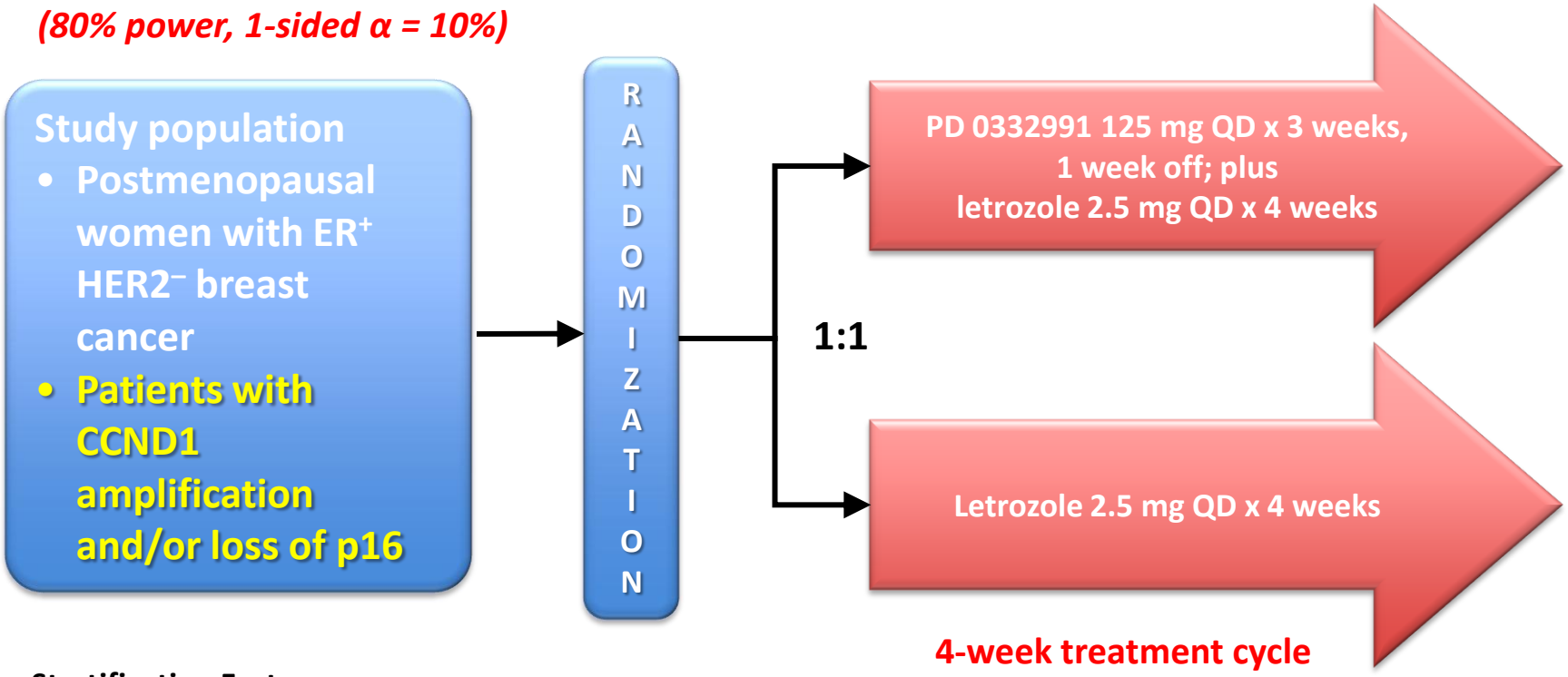
The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study

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: *Phase 2 Part 2*

Primary Endpoint: PFS

Designed to detect a 50% improvement in median PFS from 9 to 13.5 months (80% power, 1-sided α = 10%)



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

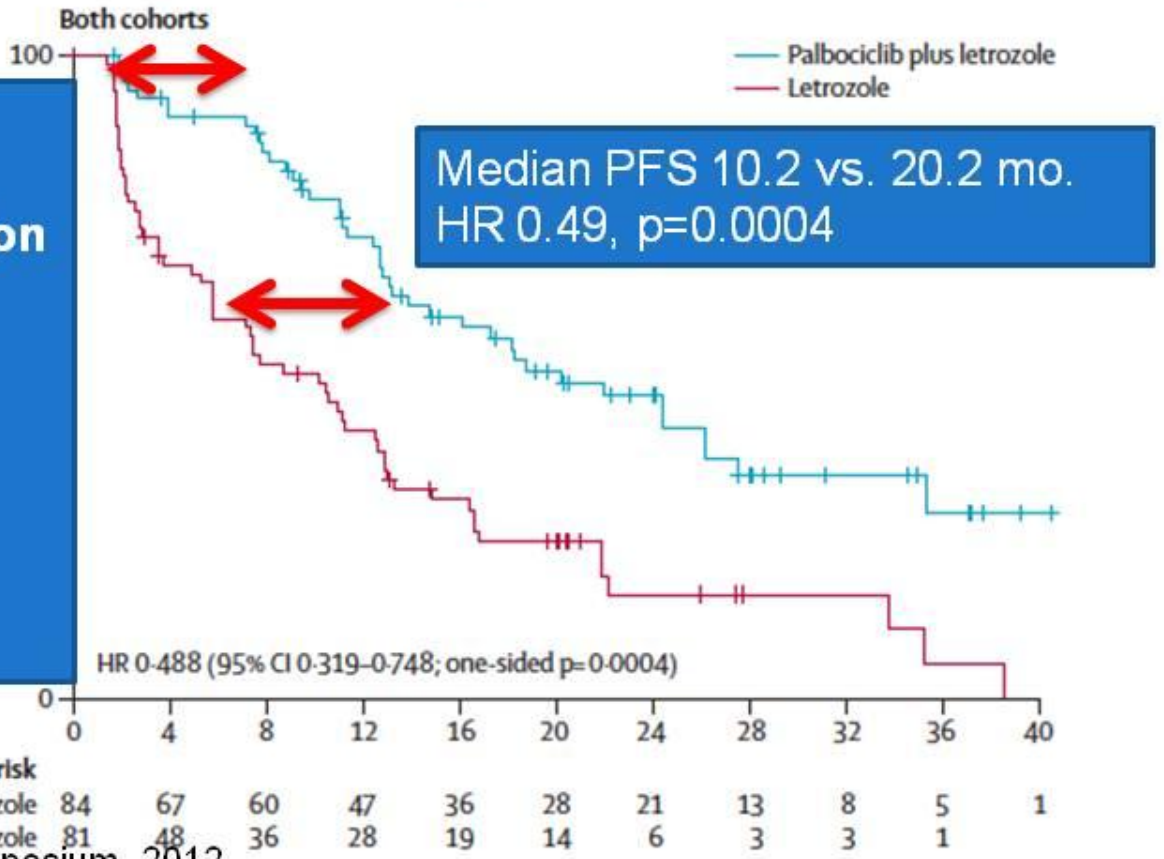
	Both cohorts		Cohort 1		Cohort 2	
	Palbociclib plus letrozole (n=84)	Letrozole (n=81)	Palbociclib plus letrozole (n=34)	Letrozole (n=32)	Palbociclib plus letrozole (n=50)	Letrozole (n=49)
Median age (years)	63 (54–71)	64 (56–70)	66 (56–72)	64 (57–70)	62 (54–70)	63 (56–71)
ECOG performance status						
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.

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

PALOMA-1: Randomized open-label phase II trial

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

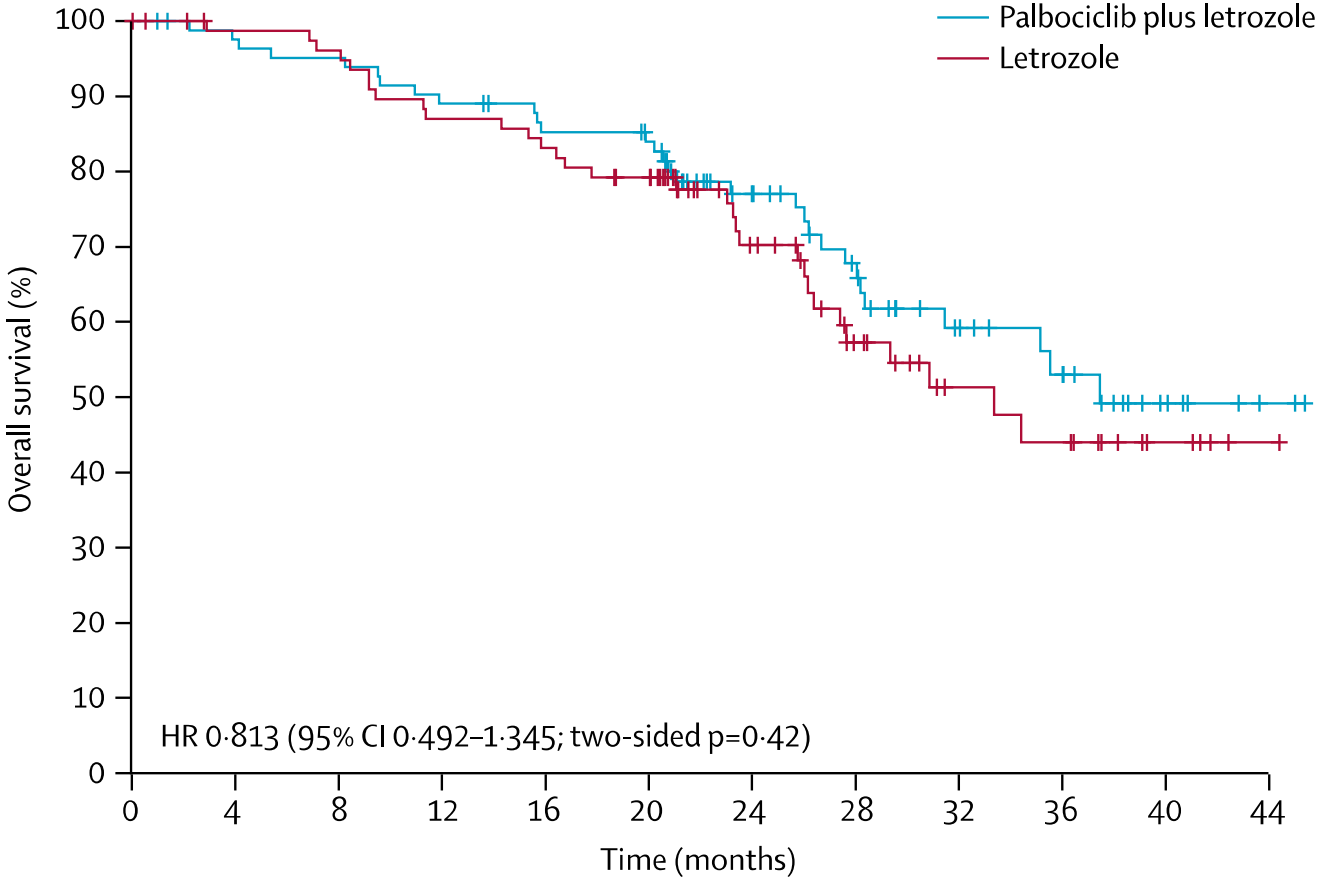


Finn et al. San Antonio Breast Cancer Symposium, 2012
Finn et al. AACR, 2014; Finn et al. Lancet Oncol, 2015

PRESENTED AT: ASCO Annual '15 Meeting

Presented By Joseph Sparano at 2015 ASCO Annual Meeting

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



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

	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%

Palbociclib in HR+/HER2– BC: Phase III Studies

	Metastatic Breast Cancer			Post-Neoadjuvant
Study	**1008 (PALOMA-2)**	**1023 (PALOMA-3)**	**PEARL**	**PENELOPE**
Setting	Endocrine sensitive	Endocrine resistant	Endocrine resistant	High risk
Menopausal status	Postmenopausal	Premenopausal + postmenopausal	Postmenopausal	Premenopausal + postmenopausal
No. of patients	650	521	348	800
Treatment	Palbociclib + letrozole vs placebo + letrozole	Palbociclib + fulvestrant vs placebo + fulvestrant	Palbociclib + exemestane vs capecitabine	Palbociclib vs placebo
Primary endpoint	PFS	PFS	PFS	iDFS

Slide courtesy of Angela DeMichele,MD, MSCE

iDFS, invasive disease-free survival; PFS, progression-free survival.

Clinicaltrials.gov.Paloma 2: NCT01740427, Paloma 3: NCT 01942135; Pearl: NCT02028507 Penelope: NCT01864746

The NEW ENGLAND JOURNAL of MEDICINE


ORIGINAL ARTICLE

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.B., B.S., 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.

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

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

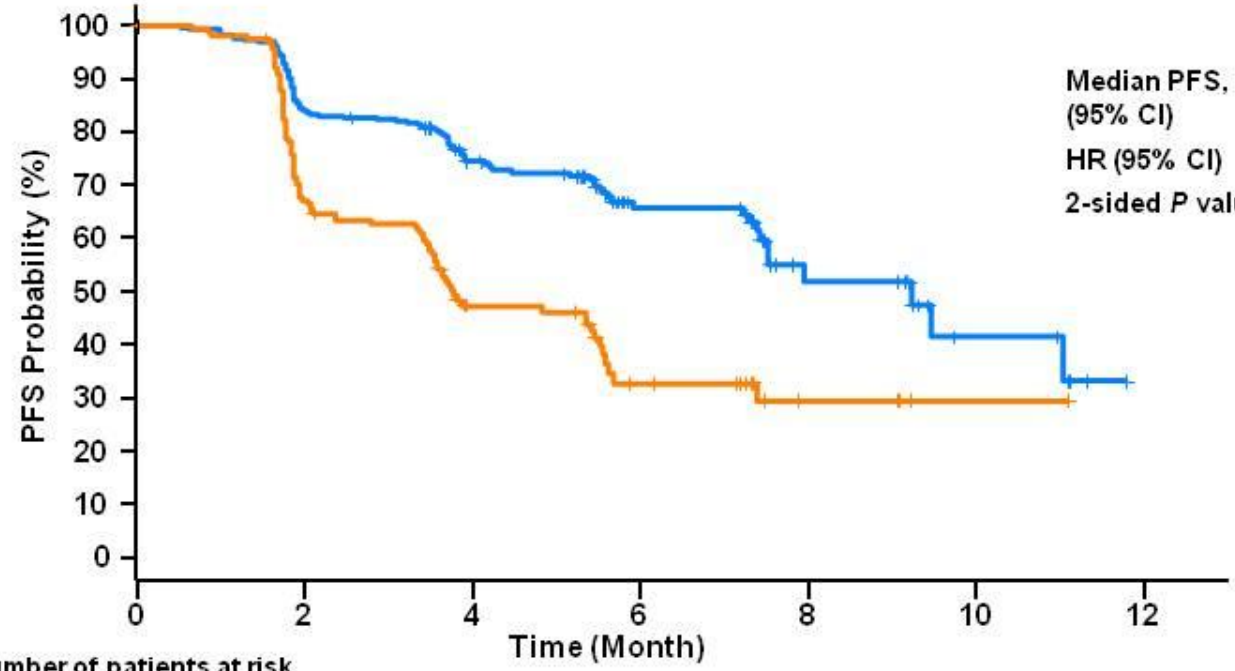
[a]Based on randomization; [b]lung, liver, brain, pleural, and peritoneal involvement.

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)



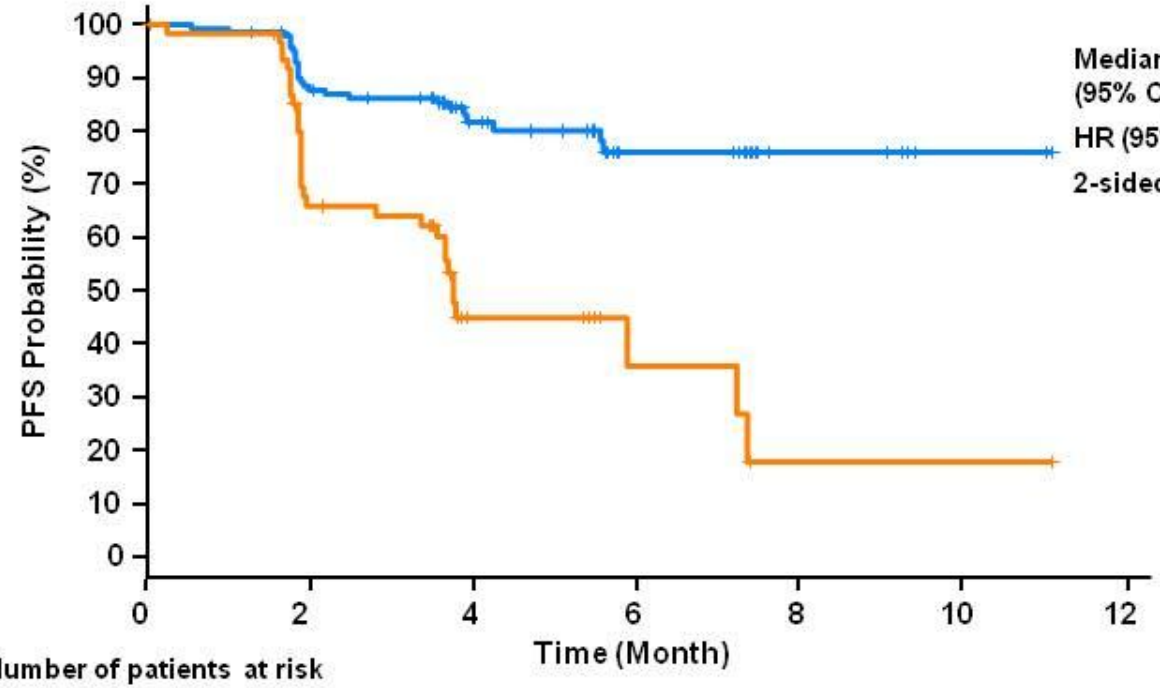
	Palbociclib + Fulvestrant n=347	Placebo + Fulvestrant n=174
Median PFS, months (95% CI)	9.2 (7.5, NE)	3.8 (3.5, 5.5)
HR (95% CI)	0.422 (0.318, 0.560)	
2-sided *P* value	<0.000001	

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.

PFS: Central Blinded Review Audit (n=211)



	Palbociclib + Fulvestrant n=147	Placebo + Fulvestrant n=64
Median PFS, months (95% CI)	NE	3.7 (3.4, 7.2)
HR (95% CI)	0.268 (0.158, 0.455)	
2-sided *P* value	<0.000001	

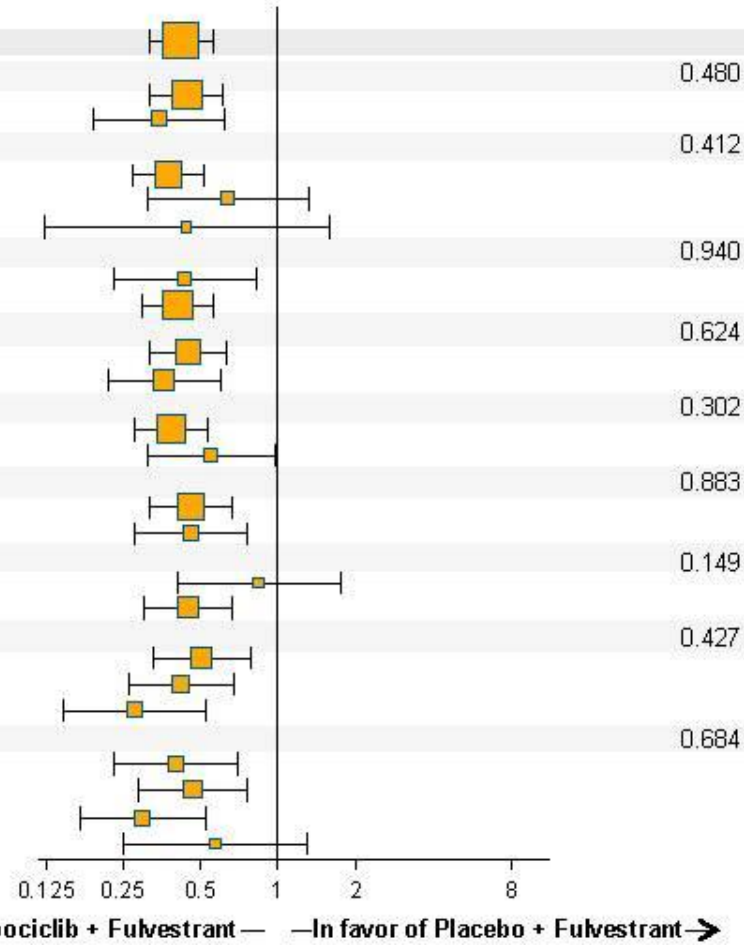
Number of patients at risk

PAL+FUL	147	118	53	24	7	2
PCB+FUL	64	37	12	4	1	1

CI=confidence interval; NE=not estimable; PFS=progression-free survival.

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%)**

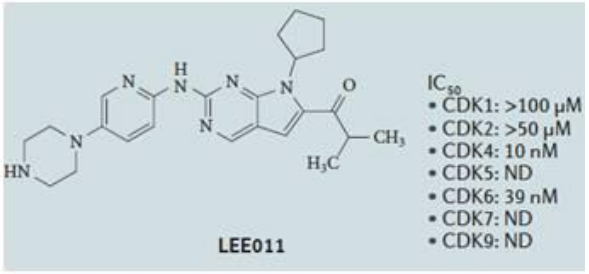
*ITT population.
AE=adverse event; AT=as treated.

Conclusions

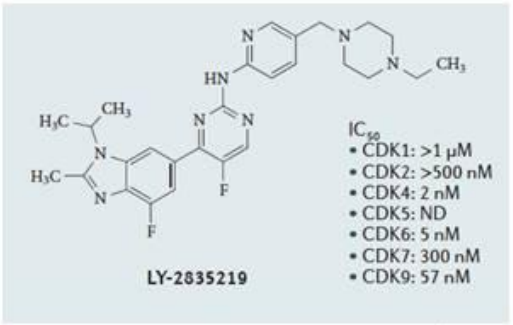
- **Palbociclib combined with fulvestrant improved PFS compared to placebo and fulvestrant in women with HR+/HER2– advanced breast cancer whose disease had progressed on prior endocrine therapy.**
  - **HR = 0.422 (95% CI, 0.318 to 0.560; *P*<0.000001)**
- **Benefit from palbociclib was also demonstrated across pre-specified subgroups.**
- **Palbociclib was well tolerated.**
- **Palbociclib in combination with fulvestrant is an effective treatment option for women whose cancer progressed on prior endocrine therapy.**

Other CDK Inhibitors in Phase III Trials in Advanced ER-Positive Breast Cancer

- Ribociclib (LEE011)
  - MONALEESA-2 (NCT 01958021) – postmenopausal - letrozole +/- ribociclib
  - MONALEESA-3 (NCT02422615) – postmenopausal - fulvestrant +/- ribociclib
  - MONALEESA-7 (NCT02278120) – premenopausal – endocrine Rx +/- ribociclib



- Abemeciclib (LY2835219)
  - MONARCH 2 (NCT 02107703) – postmenopausal - fulvestrant +/- abemeciclib
  - MONARCH 3 (NCT 02246621) – postmenopausal – non-steroidal A.I +/- abemeciclib



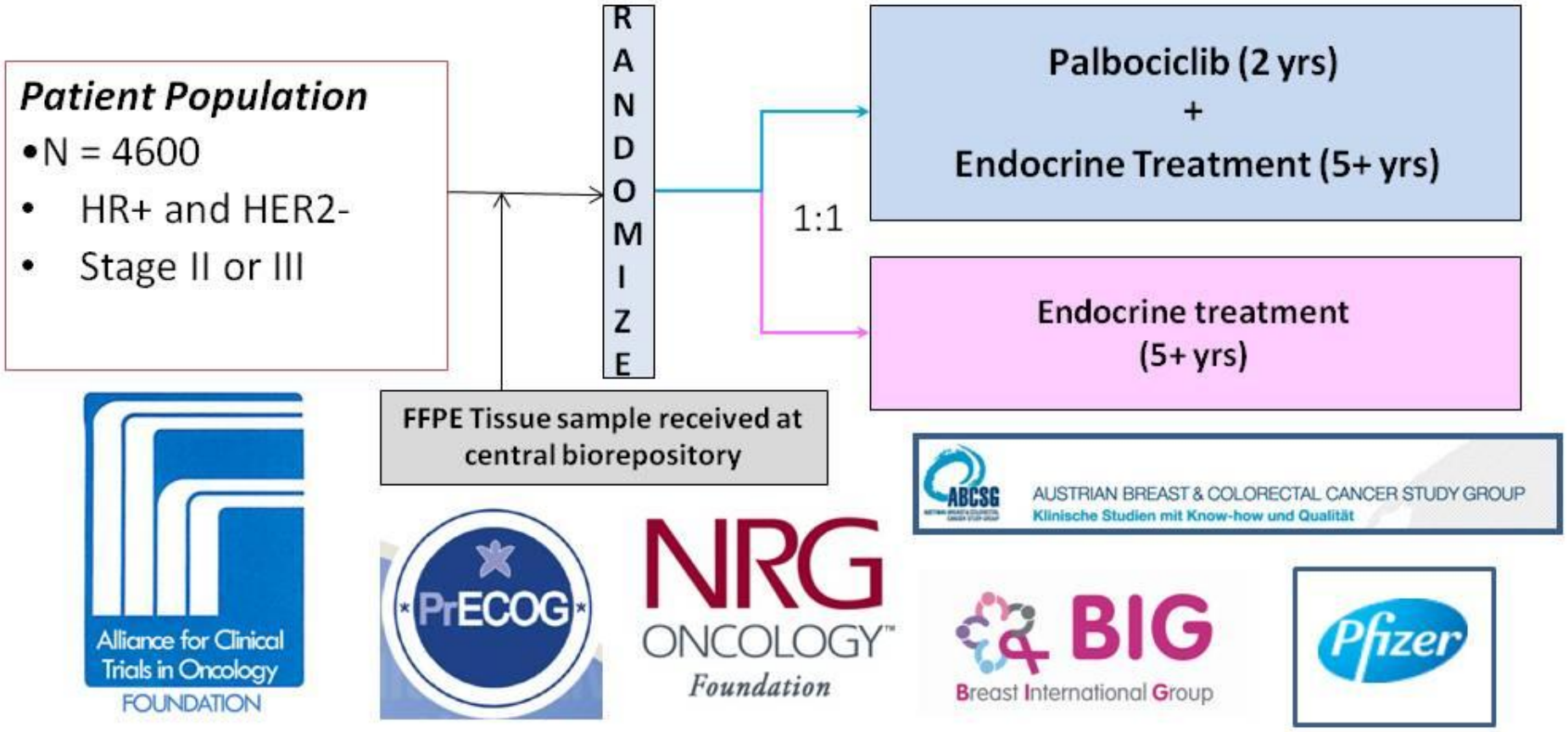
Source of information: ClinicalTrials.gov (accessed 5/31/15)

PRESENTED AT: ASCO Annual '15 Meeting

TREND

Phase 2, open-label, multicenter, randomized study of PD 0332991 (oral CDK 4/6 inhibitor) monotherapy and PD 0332991 in combination with the endocrine therapy to which the patient has progressed in the previous line for ER-positive, HER2-negative post-menopausal advanced breast cancer patients.

PALbociclib CoLlaborative Adjuvant Study (PALLAS)



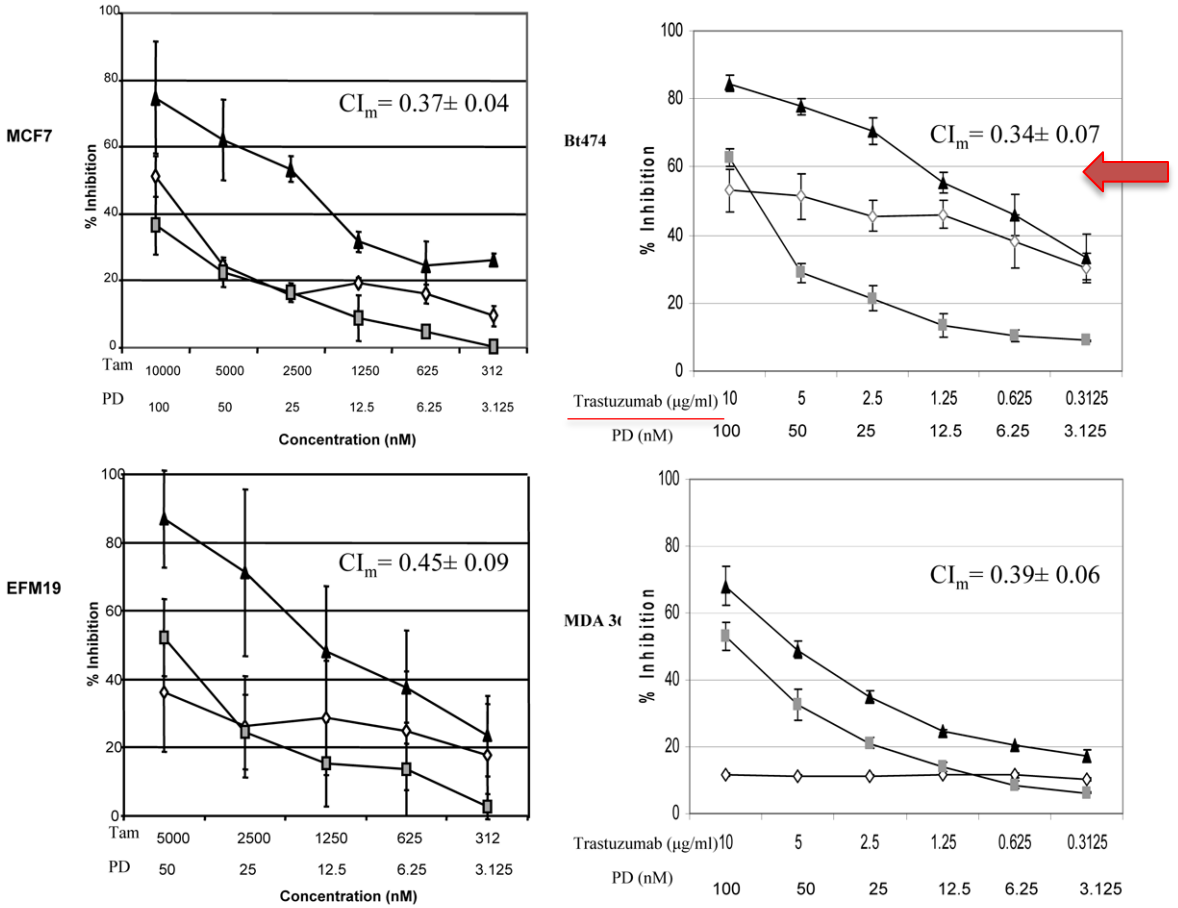
Presented By Joseph Sparano at 2015 ASCO Annual Meeting

Research article

PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines *in vitro*

Richard S Finn[1], Judy Dering[1], Dylan Conklin[1], Ondrej Kalous[1], David J Cohen[1], Amrita J Desai[1], Charles Ginther[1], Mohammad Atefi[1], Isan Chen[2], Camilla Fowst[3], Gerret Los[2] and Dennis J Slamon[1]

Combinations of PD 0332991 plus tamoxifen and PD 0332991 plus trastuzumab in ER-positive and HER2-amplified breast cancer cells, respectively



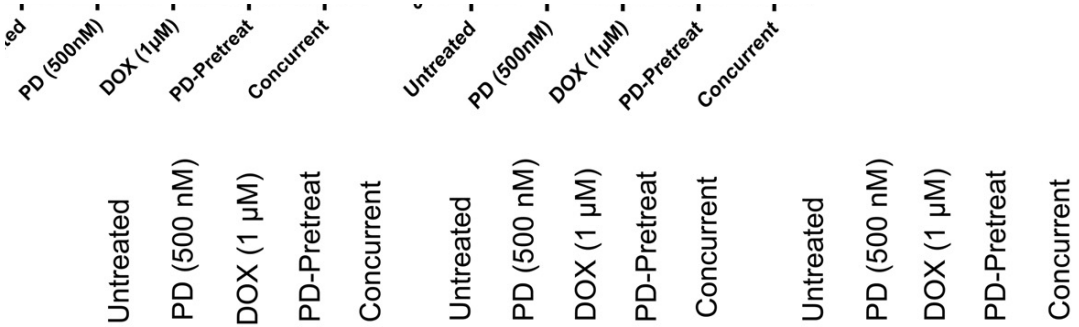
Cell Biology:

Modification of the DNA Damage Response by Therapeutic CDK4/6 Inhibition

Jeffry L. Dean, A. Kathleen McClendon and
Erik S. Knudsen

- recent evidence has suggested a role for E2F-mediated gene transcription in DNA damage response and repair, as well as apoptosis signaling.
- repression of E2F activity via CDK4/6 inhibition and RB activation impacts the response of triple negative breast cancer (TNBC) to frequently used therapeutic agents.

- **CDK4/6 inhibition can antagonize cytotoxic therapeutic strategies and increases utilization of error-prone DNA repair mechanisms that could contribute to disease progression.**



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 Paloma-1/TRIO-18 trial, patients selection on the basis of cyclin D1 amplification or p16 loss was not associated with an improved outcome from palpociclib

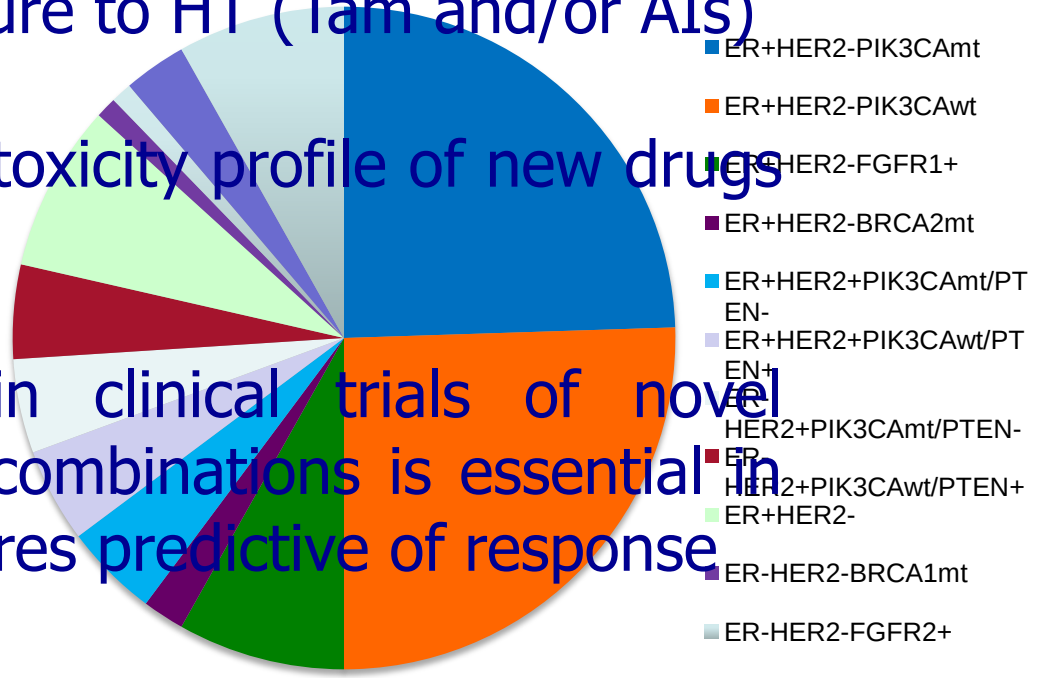
- one of the most important markers of sensitivity to palbociclib is the presence of an intact Rb pathway; however, since pRb loss is uncommon in oestrogen receptor-positive, HER2-negative breast cancers, it was not used as a prospective independent biomarker for patient selection in the present study.

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

COMPLEXITY OF BC

Breast Cancer 2013

Breast Cancer 2016



Impact of prior exposure to HT (Tam and/or AIs)

Attention to different toxicity profile of new drugs and quality of life

Biomarker analysis in clinical trials of novel targeted agents and combinations is essential in order to identify features predictive of response

Adapted from Fabrice Andre