Incontri di aggiornamento del Dipartimento Oncologico

Oncologia traslazionale: nuove vie del segnale e nuovi inibitori (1° edizione)

IL BLOCCO DEL CICLO CELLULARE: INIBITORI DELLE CHINASI CICLINO-DIPENDENTI

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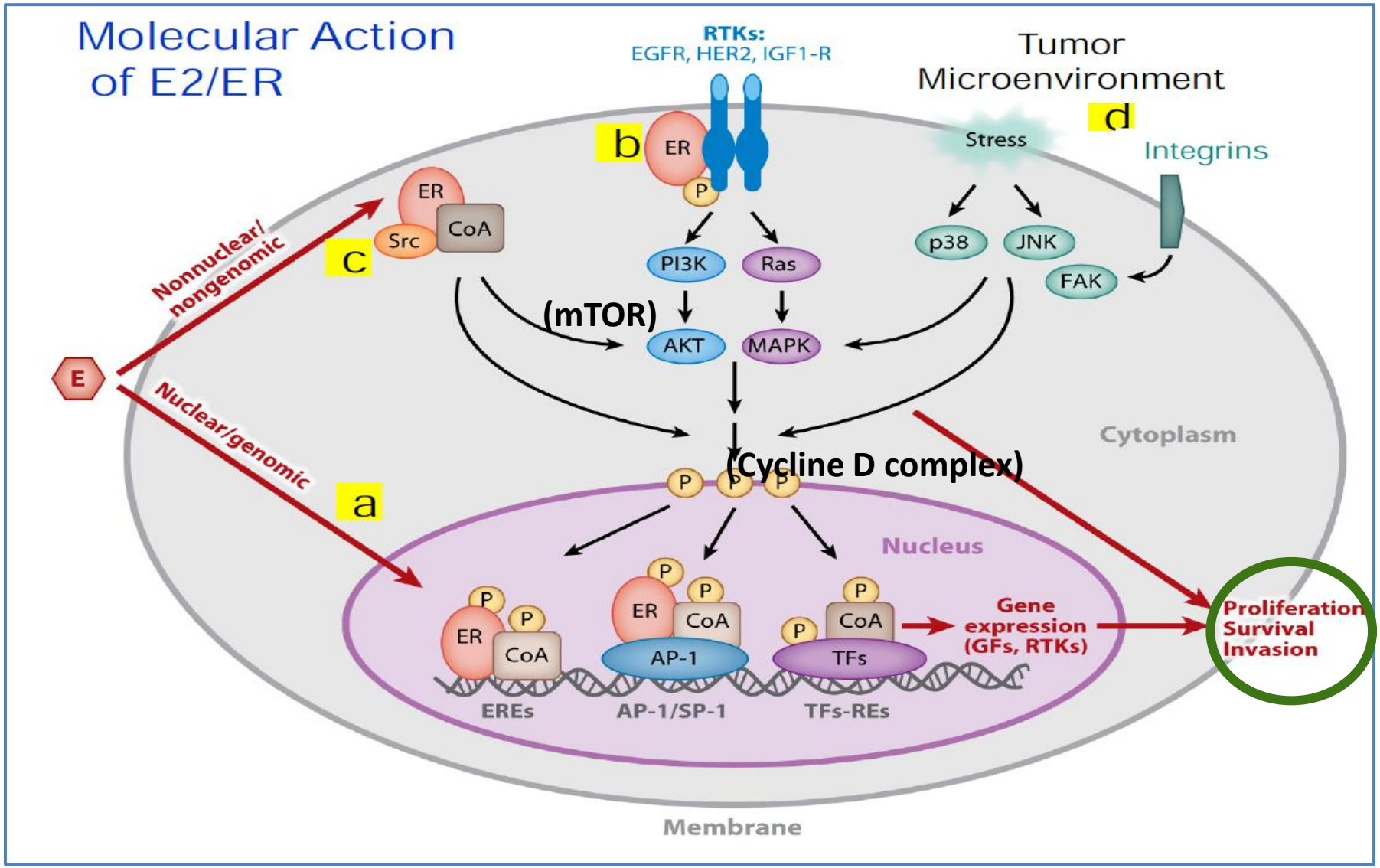
11 Novembre 2015

HR+ in 70% of breast cancers with prognostic and predictive role



ER discovery

Tamoxifen

Anastrozole

Letrozole
Exemestane
Fulvestrant

Palbociclib
(antiCD4/6)

Prognostic and Predictive Role

ER assay (DCC)

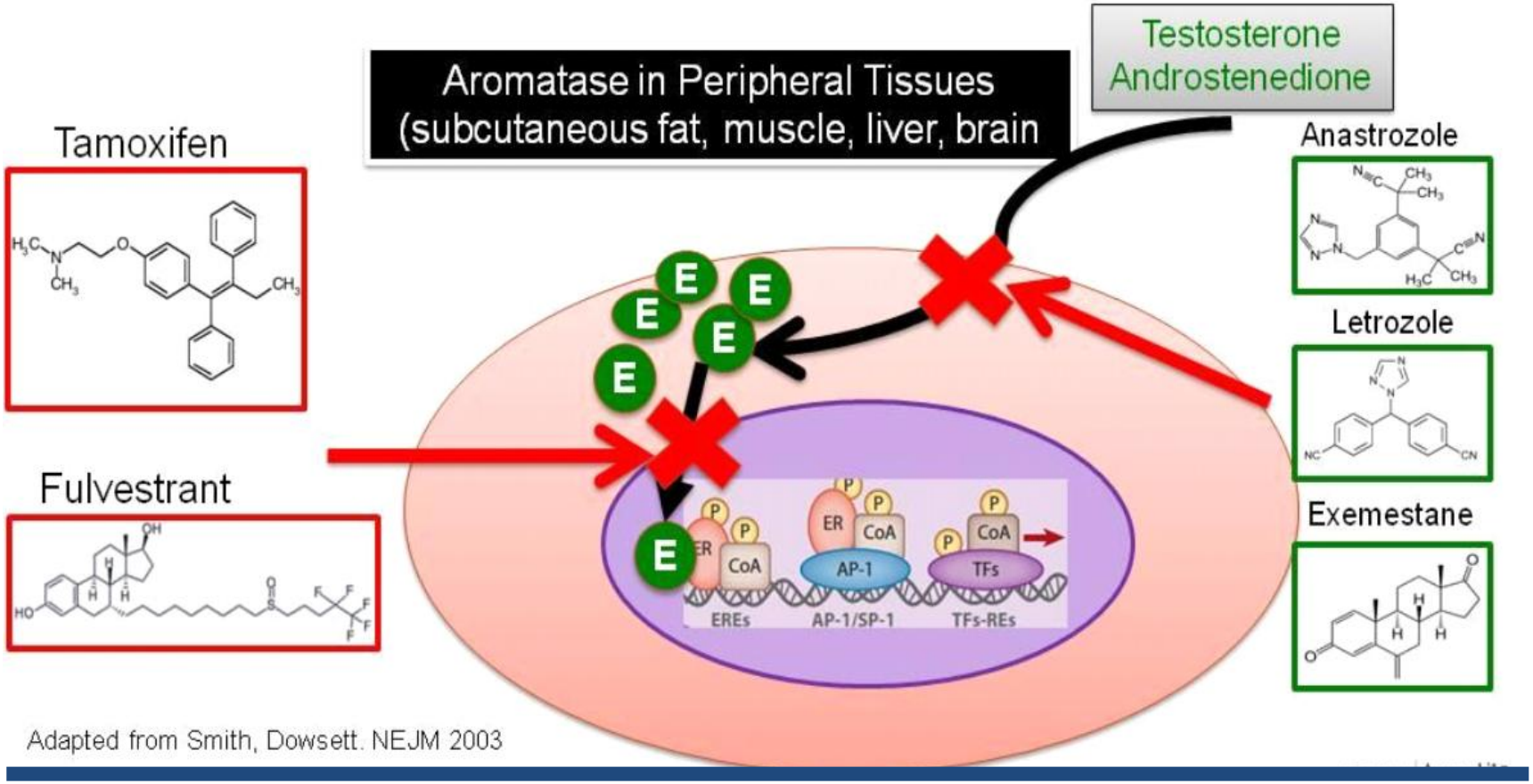
ESR1 cloning

ER assay (ICH)

Everolimus
(mTOR inhibitor)

ESR1 mutations

1970 1980 1990 2000 2010 2015



* Aromatase inhibitors

** "SERMs"-Selective Estrogen-Receptors Modulator

*** Estrogen receptor antagonist (accelerates the proteosomal degradation of ER)

Crosstalk between ER and mTOR Signaling

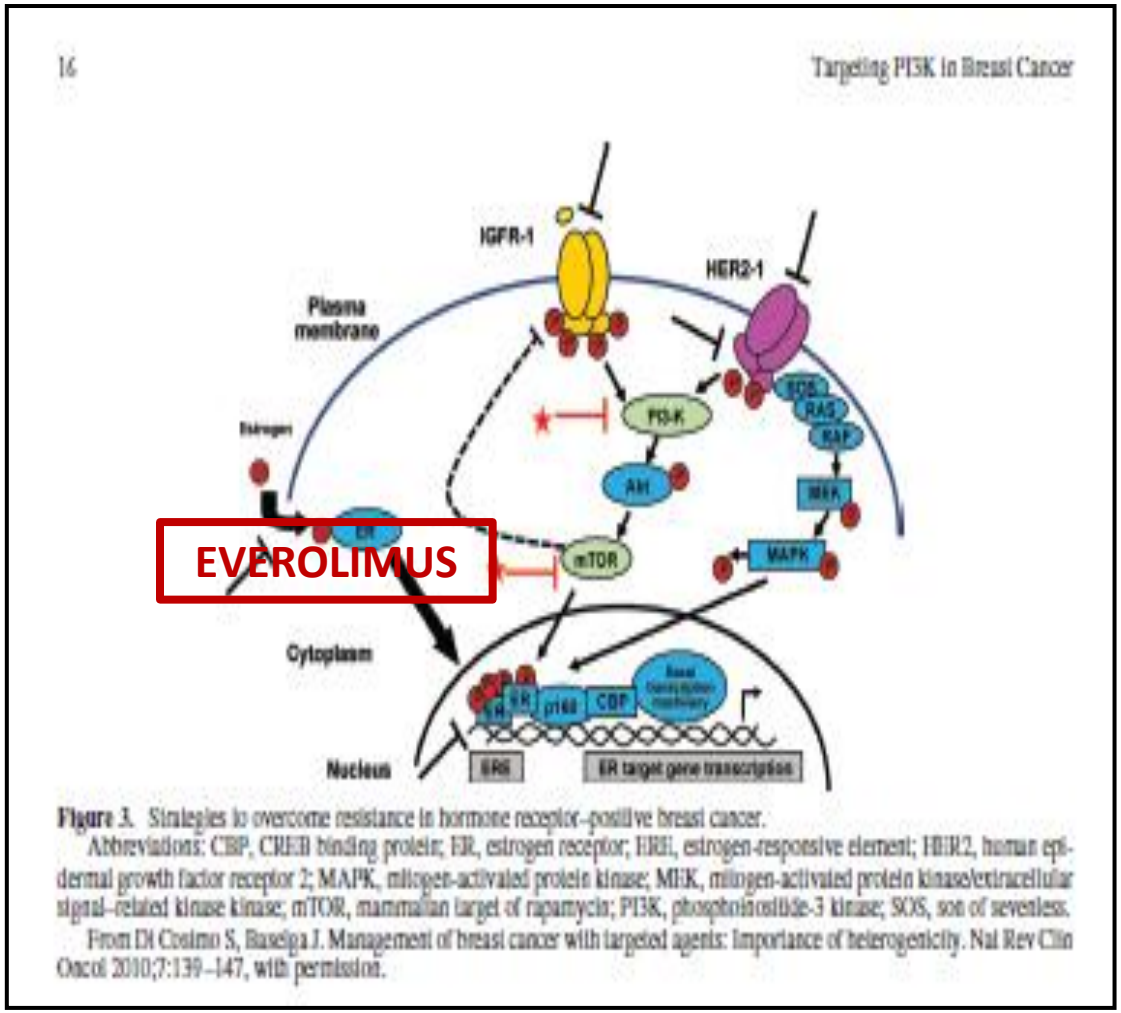
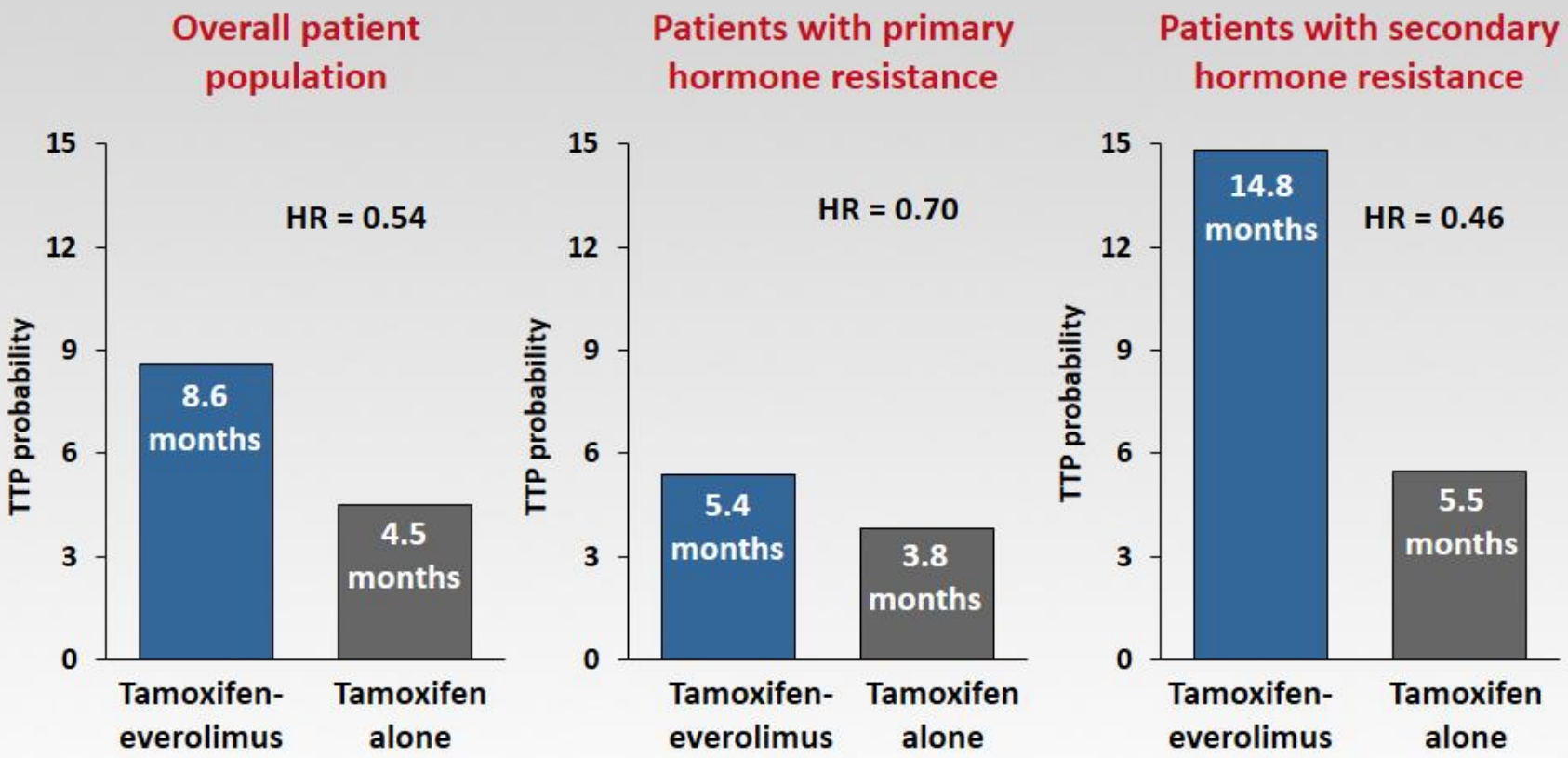


Figure 3. Strategies to overcome resistance in hormone receptor–positive breast cancer.
Abbreviations: CBP, CREB binding protein; ER, estrogen receptor; ERE, estrogen-responsive element; HER2, human epidermal growth factor receptor 2; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase/extracellular signal–related kinase kinase; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide-3 kinase; SOS, son of sevenless.
From Di Cosimo S, Baselga J. Management of breast cancer with targeted agents: Importance of heterogeneity. Nat Rev Clin Oncol 2010;7:139–147, with permission.

The Oncologist 2011;16(suppl 1):12–19

- **mTORC1 activates ER in a ligand-independent fashion[1]**
- **Estradiol suppresses apoptosis induced by PI3K/mTOR blockade[2]**
- **Hyperactivation of the PI3K/mTOR pathway is observed in endocrine-resistant breast cancer cells[3]**
- **mTOR is a rational target to enhance the efficacy of hormonal therapy**

Response to Therapy in Patients With Primary and Secondary Hormone Resistance

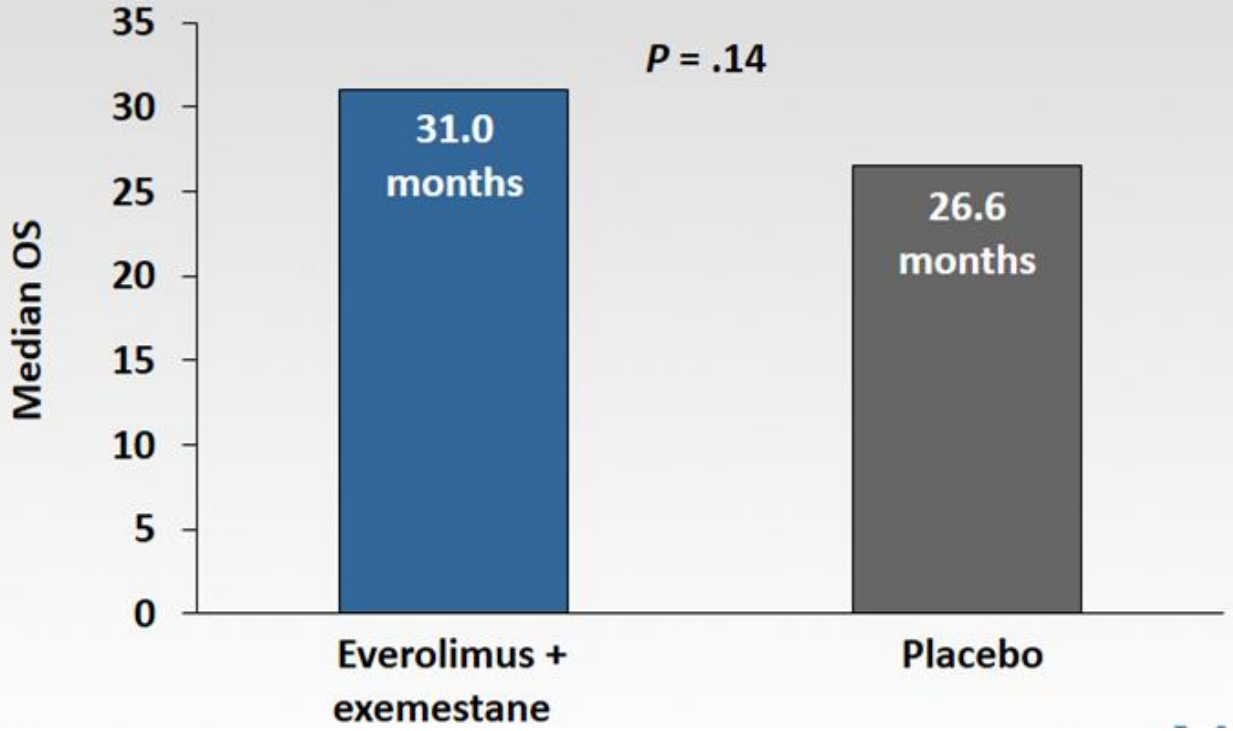


"TAMRAD" TRIAL

Bachelot T et al, J Clin Oncol, 2008

Adding Everolimus to Exemestane After Recurrence or Progression on NSAI: BOLERO 2

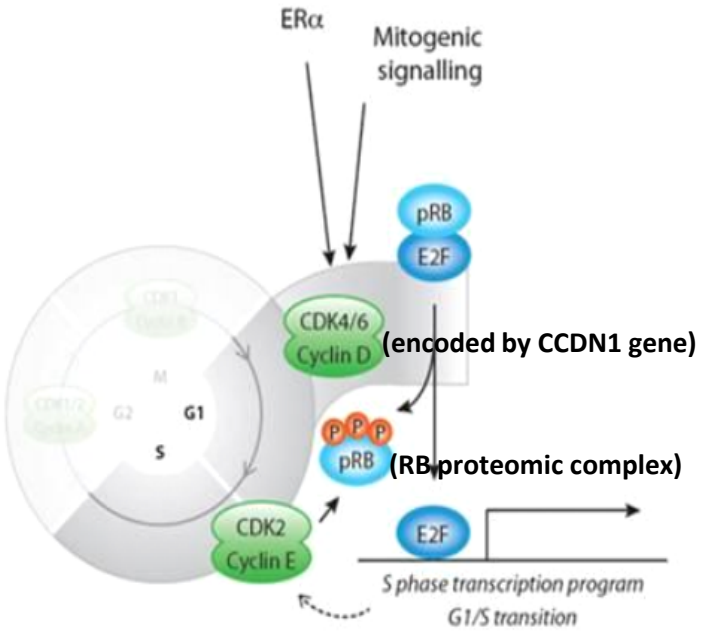
- **Patients with HR-positive, HER2-negative ABC (410 deaths; 13 patients still on treatment)**



Piccart M, et al. *Ann Oncol.* 2014;25(12):2357-2362.

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]**



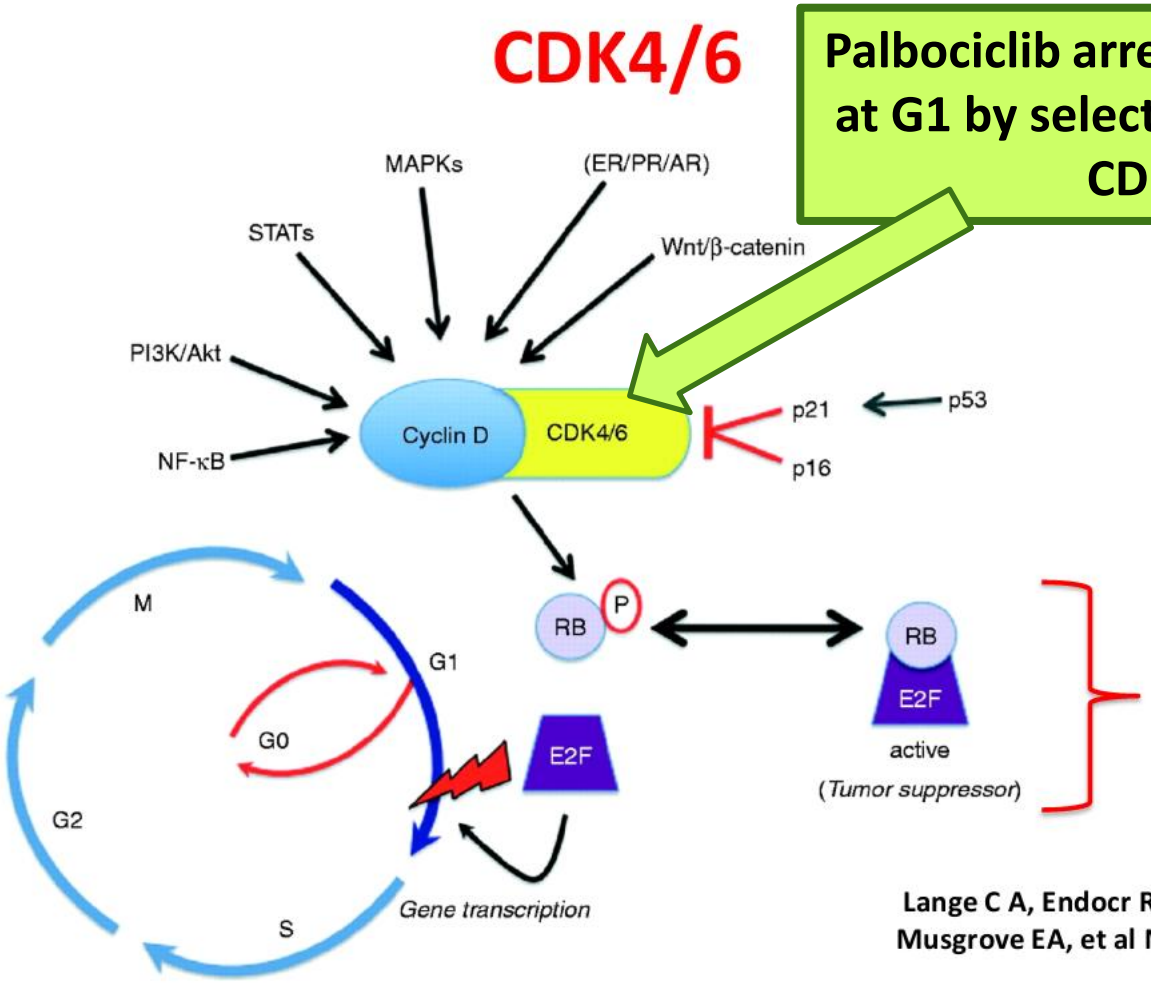
CDK=cyclin-dependent kinase; ER=estrogen receptor; HR+=hormone receptor-positive.

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.

CDK INHIBITORS IN PHASE III TRIALS IN ADVANCED ER-POSITIVE BREAST CANCER

- Palbociclib – «PALOMA» trials
- Ribociclib – «MONALEESA» trials
- Abemaciclib – «MONARCH» trials

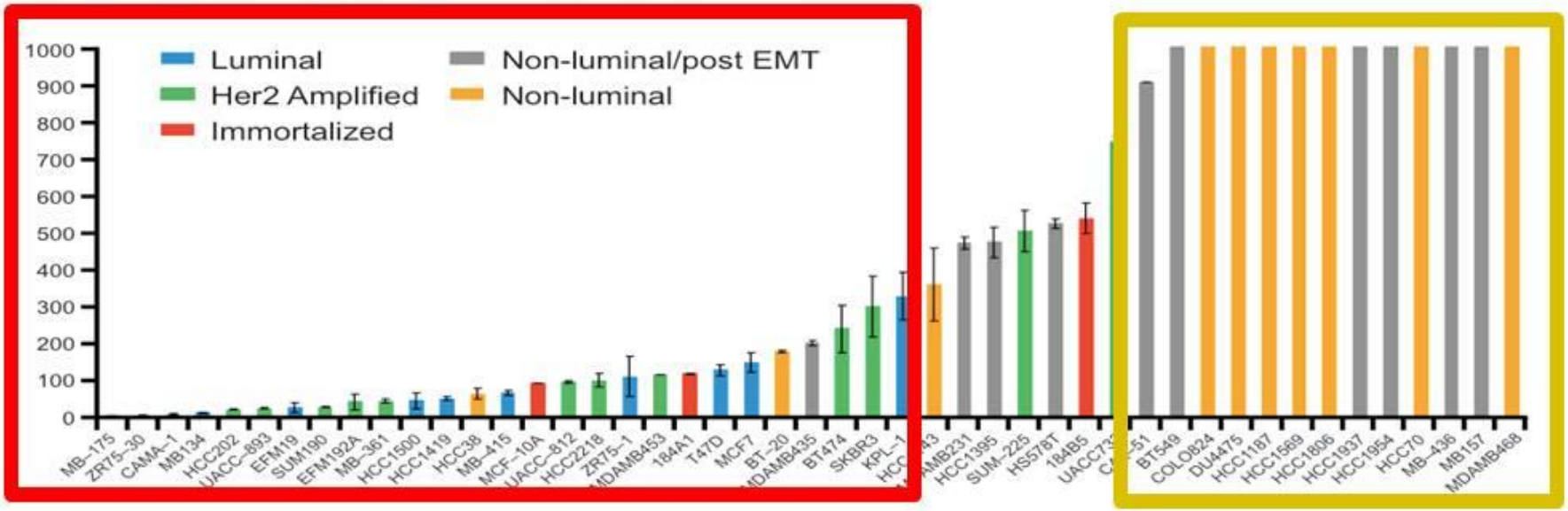
Palbociclib Mechanism of Action: selective CDK4/6 Inhibition



pRb phosphorylation and inactivation

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

Palbociclib Inhibits Luminal ER+ Human Breast Cancer Cell Lines In Vitro



Sensitive cells – intact RB protein

Finn RS, et al. *Breast Cancer Res.* 2009;11(5):R77.

Palbociclib is a potent and highly selective reversible inhibitor of CDK4/6 that prevents cellular DNA synthesis by prohibiting progression of the cell cycle from G1 into the S phase through blocking Rb phosphorylation.

Preclinical and clinical data suggest that luminal ER-positive subtype are sensitive to CDK4/6 inhibition. In addition, synergy with endocrine therapy has been demonstrated.

- **Oral, highly selective inhibitor of CDK4/6**
- **Prevents cell-cycle progression from G1 to S phase**
- **In vitro activity in Rb-positive tumor cell lines and primary tumors**
- **Low nanomolar concentrations block Rb phosphorylation inducing G1 arrest in sensitive cell lines**

WHAT'S 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]

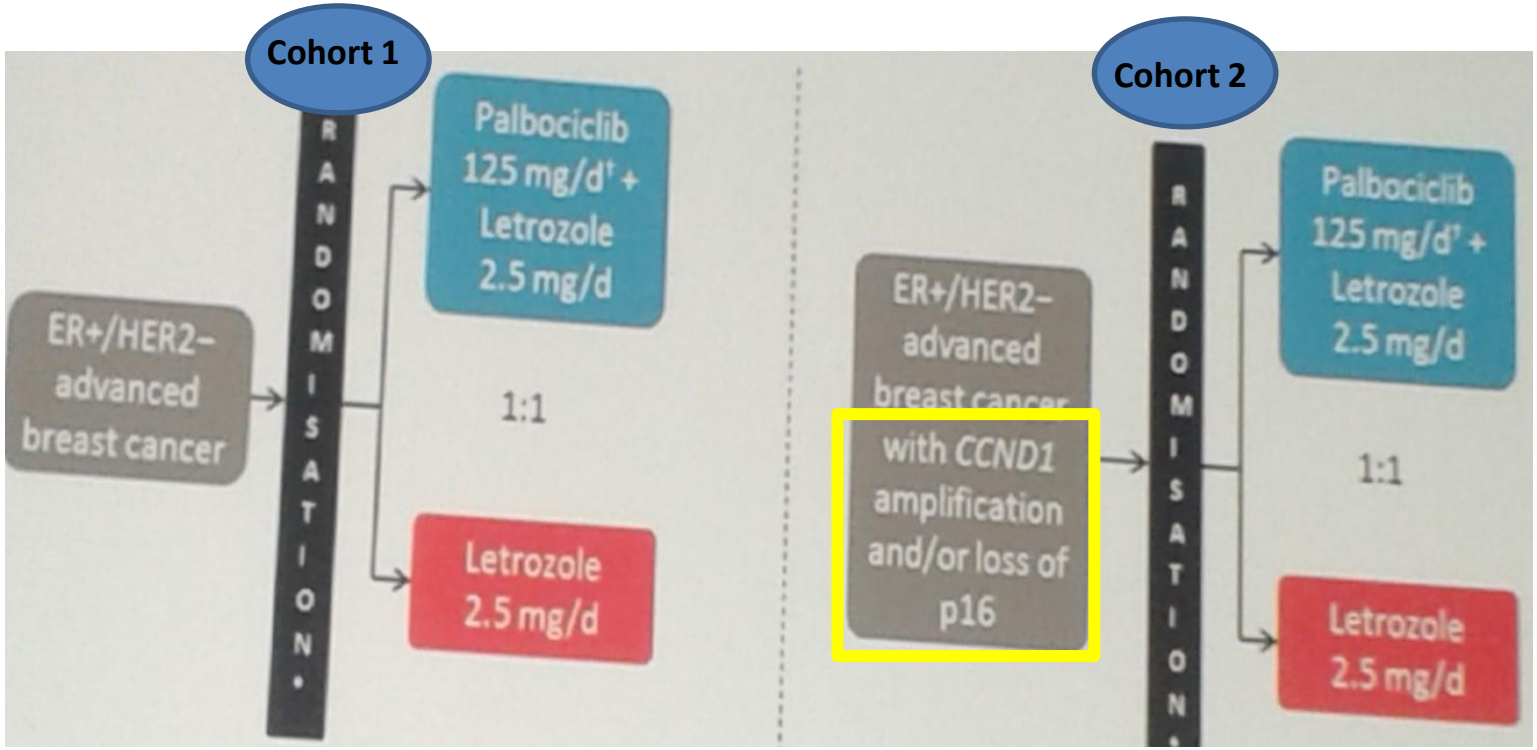
1)Toogood J Med Chem 2005; 2) Finn Breast Cancer Res 2009

Recent data from clinical trials suggest that palbociclib has activity when combined with endocrine therapy in both patients who have no previously received endocrine therapy and those who have disease that is resistant to such therapy.

Paloma -1 Study Design

Randomized phase II open-label trial involving 50 centres in 12 countries

Endpoints: Primary PFS; Secondary: ORR, OS, clinical benefit response, duration of response, safety and tollerability, serum biomarker analyses



(4 –week cycles)

Elegibility criteria

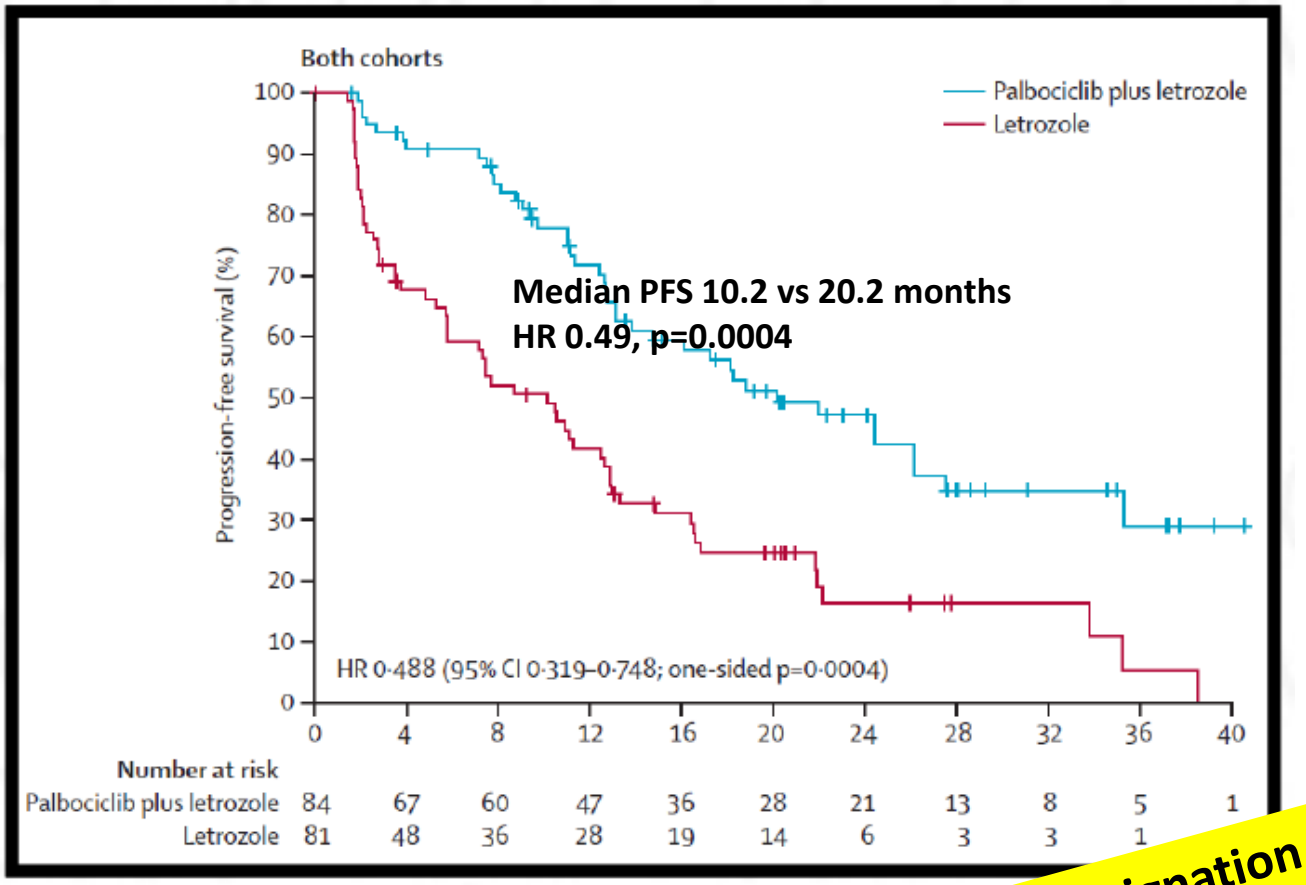
Inoperable, locally recurrent disease; postmenopausal status, no prior therapy for advanced cancer, no letrozole within 12 months, ECOG performance status ≤1

	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)**

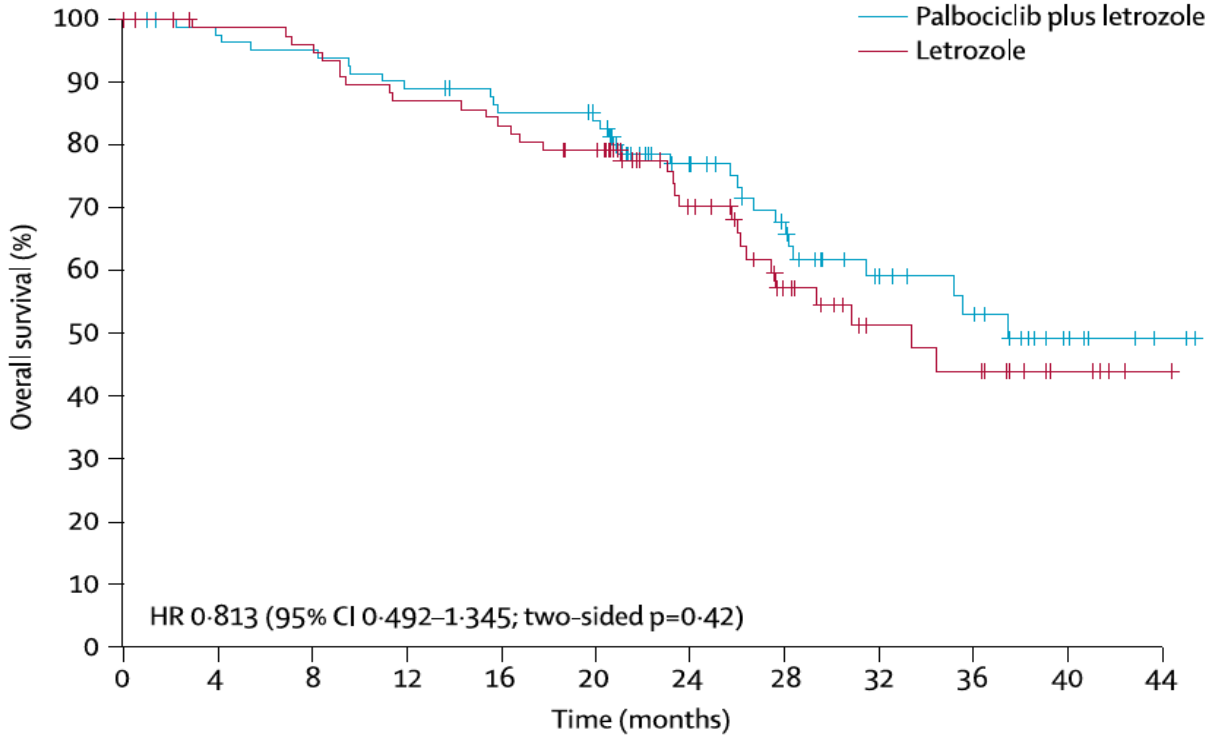
PALOMA-1



FDA Breakthrough Designation April 2013
Accelerated FDA approval February 2015

Finn RS et al, Lancet Oncol 2015; 16 (1): 25

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

With 30 events in the Palbociclib+Letrozole arm and 32 events in the control arm, study failed to demostrate an OS advantage by adding Palbociclib. A follow up OS analysis will be performed after the accrual of additional events.

PALOMA – 1: Conclusion

- The data from this study demonstrate the activity and safety of CDK 4/6 inhibition in the first-line setting in patients with ER+/HER2– advanced breast cancer
  - Palbociclib plus letrozole significantly prolonged PFS, irrespective of cyclin D1 and p16 alterations
  - Objective response rate (43% vs 33%) and clinical benefit rate (81% vs 58%) were also substantially improved, confirming the clinical benefit of this combination
  - Initial assessment of OS shows no significant difference between arms; a follow-up analysis of OS will be conducted following additional events
- Palbociclib plus letrozole had a clinically manageable toxicity profile
  - The most common adverse event was uncomplicated neutropenia, likely due to an on-target side effect of palbociclib

Finn RS et al, Lancet Oncol 2015; 16 (1): 25

Abstract LBA502

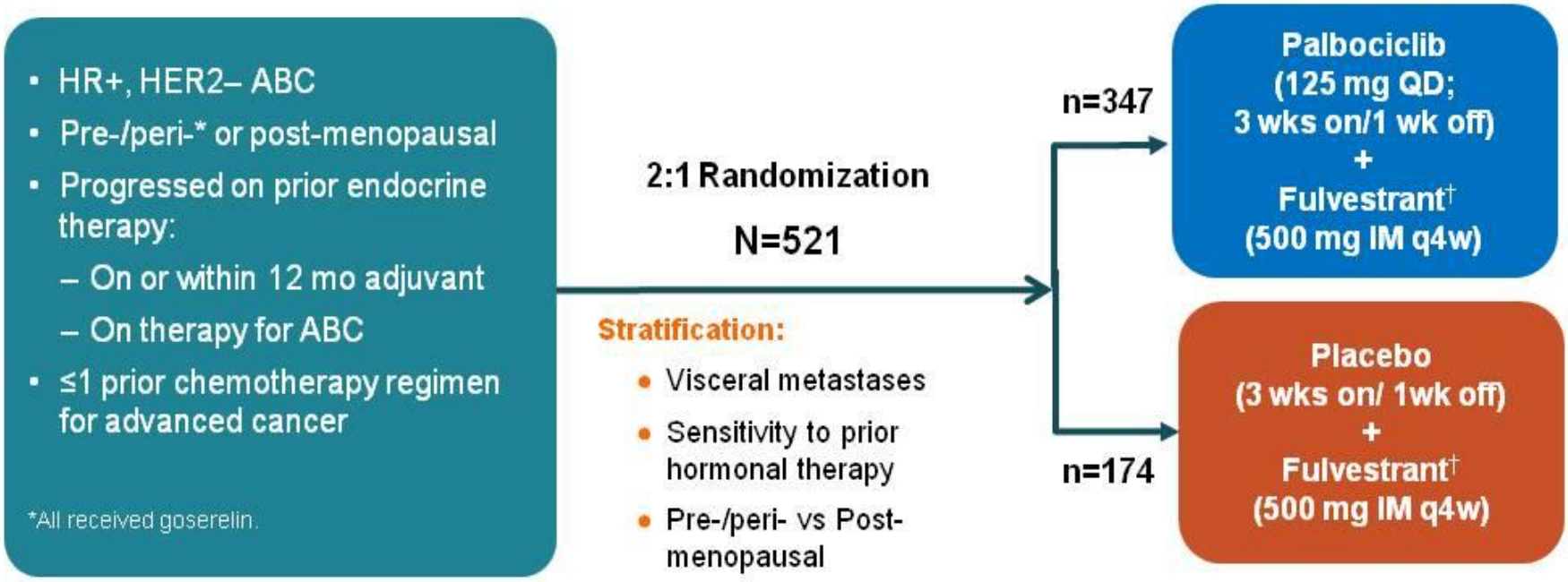
A Double Blind Phase 3 Trial of Fulvestrant With or Without Palbociclib in Pre- and Post-menopausal Women With Hormone Receptor-positive, HER2-negative Advanced Breast Cancer That Progressed on Prior Endocrine Therapy (PALOMA3 Study)

Nicholas Turner,[1] Jungsil Ro,[2] Fabrice André,[3] Sherene Loi,[4] Sunil Verma,[5] Hiroji Iwata,[6] Nadia Harbeck,[7] Sibylle Loibl,[8] Cynthia Huang Bartlett,[9] Ke Zhang,[10] Carla Giorgetti,[11] Sophia Randolph,[10] Maria Koehler,[9] Massimo Cristofanilli[12]

[1]Royal Marsden Hospital, London, UK; [2]National Cancer Center, Goyang-si, Korea; [3]Institut Gustave Roussy, Villejuif, France; [4]Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia; [5]Sunnybrook Odette Cancer Centre, Toronto, Canada; [6]Aichi Cancer Center Hospital, Nagoya, Japan; [7]Brustzentrum der Universität München, München, Germany; [8]German Breast Group Forschungs GmbH, Neu-Isenburg, Germany; [9]Pfizer Inc, New York City, USA; [10] Pfizer La Jolla, USA; [11]Pfizer Milan, Italy, [12]Thomas Jefferson University, Philadelphia, PA, USA

Presented at ASCO 2015; June 1, 2015; Chicago, IL, USA

PALOMA3 Study Design



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

†administered on Days 1 and 15 of Cycle 1.

Clinicaltrials.gov NCT01942135

Presented By Nicholas Turner at 2015 ASCO Annual Meeting

Study Endpoints

- Primary Endpoint
  - Progression-free survival (PFS) by investigator assessment
- Secondary Endpoints
  - Objective response and clinical benefit rate
  - Overall survival
  - Safety
  - Biomarkers
  - Patient-reported outcomes

Statistical Design

- PFS by investigator assessment
  - Median PFS from 6 to 9.38 months (HR: 0.64; 90% power, 1-sided α=2.5%)*
  - Planned 417 patients randomized and 238 PFS events
- Interim Analysis (IA) for PFS
  - Planned after approximately 60% (143) of PFS events
  - Pre-specified Haybittle-Peto efficacy boundary (1-sided α =0.00135)
- Blinded independent central review (BICR)[1]
  - Randomly selected subgroup (approximately 40%)

- Accrual: Sept 2013 to Aug 2014
- 521 patients randomized
  - 144 centers in 17 countries
  - 167 pts randomized in July 2014
- Interim analysis data cut-off: Dec 5, 2014

-At 195 PFS events, increased reflecting rapid enrollment
-Independent data monitoring committee established that the study met the primary endpoint

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.

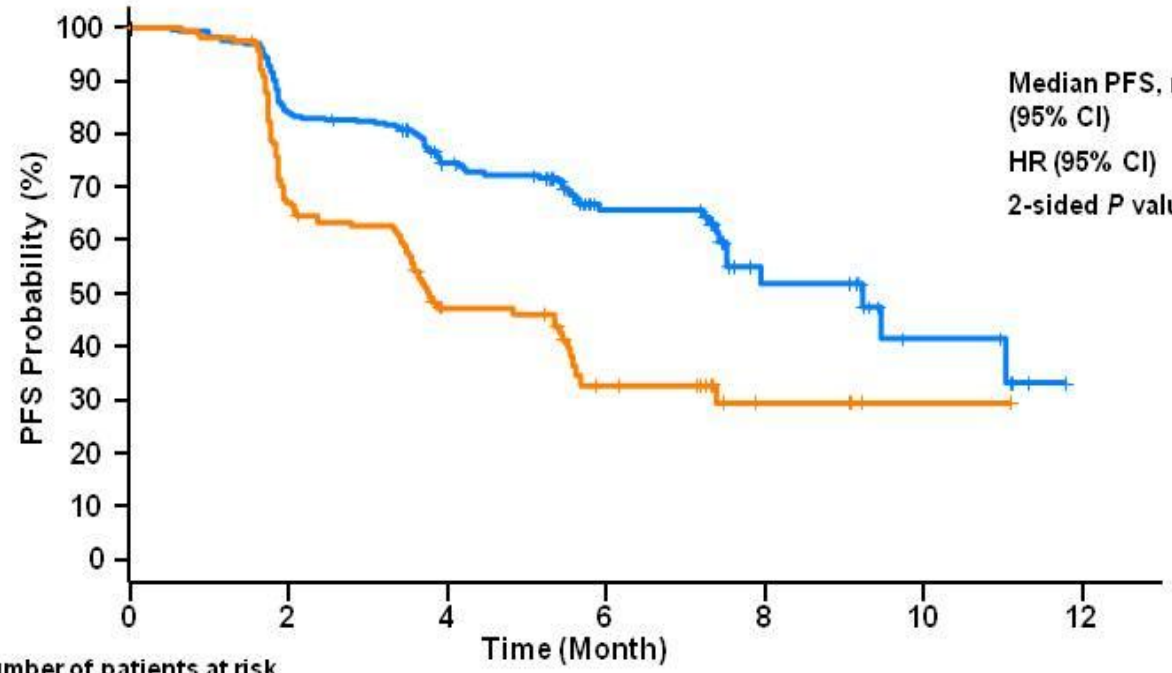
Presented By Nicholas Turner at 2015 ASCO Annual Meeting

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)



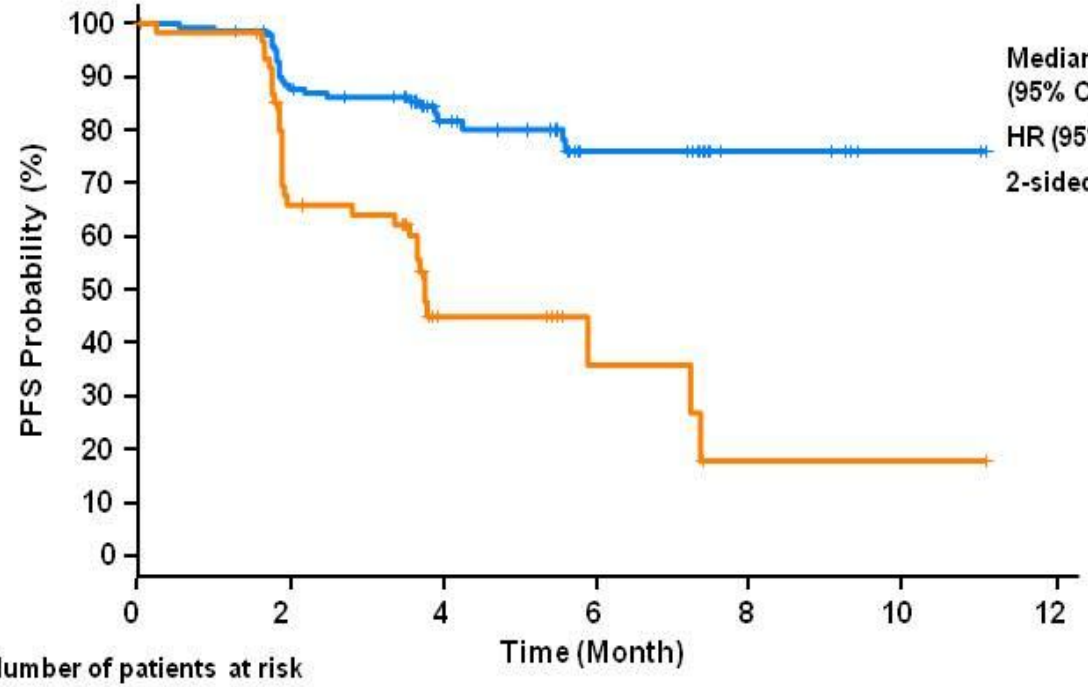
	Palbociclib + Fulvestrant n=347	Placebo + Fulvestrant n=174
Median PFS, months (95% CI)	9.2 (7.5, NE)	3.8 (3.5, 5.5)
HR (95% CI)	0.422 (0.318, 0.560)	
2-sided *P* value	<0.000001	

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

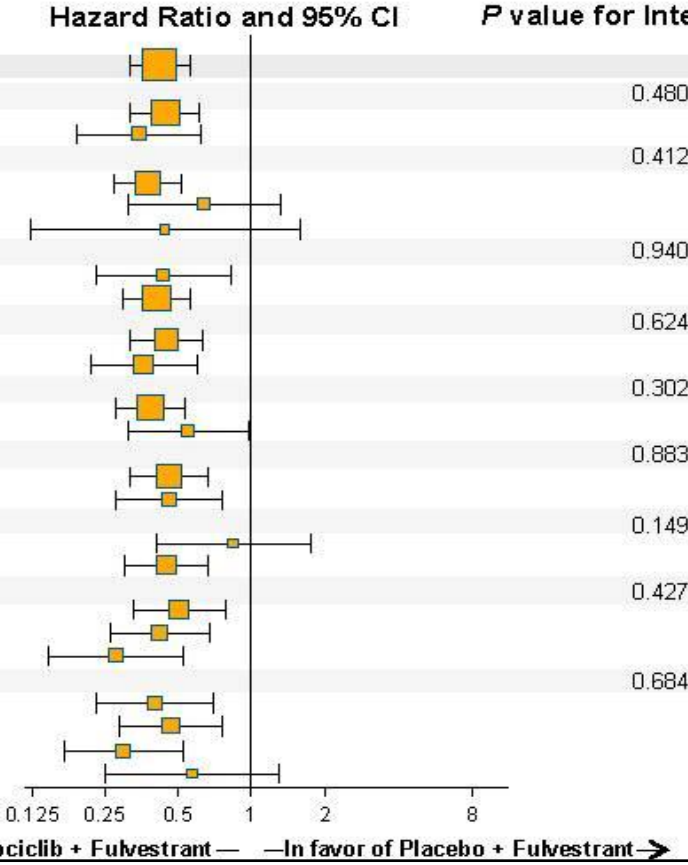
PAL+FUL	147	118	53	24	7	2
PCB+FUL	64	37	12	4	1	1

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

Presented By Nicholas Turner at 2015 ASCO Annual Meeting

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).

Conclusions

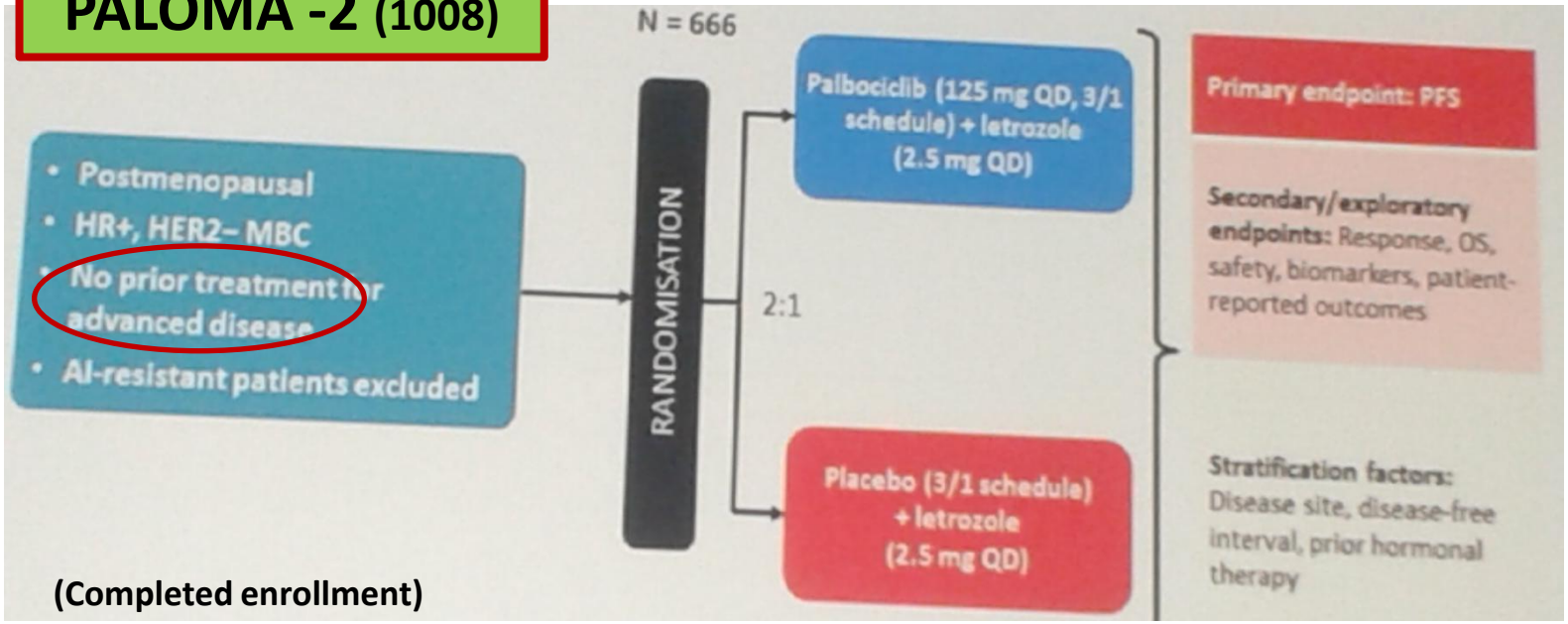
- **Palbociclib combined with fulvestrant improved PFS compared to placebo and fulvestrant in women with HR+/HER2– advanced breast cancer whose disease had progressed on prior endocrine therapy.**
  - **HR = 0.422 (95% CI, 0.318 to 0.560; *P*<0.000001)**
- **Benefit from palbociclib was also demonstrated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

(Presented by Nicholas Turner at ASCO Annual Meeting 2015)

EMA (“European Medicines Agengy”) validated marketing application of palbociclib in combination with endocrine therapy of HR+/HER2- metastatic breast cancer based on final results of “PALOMA-1” and “PALOMA-3” trials.

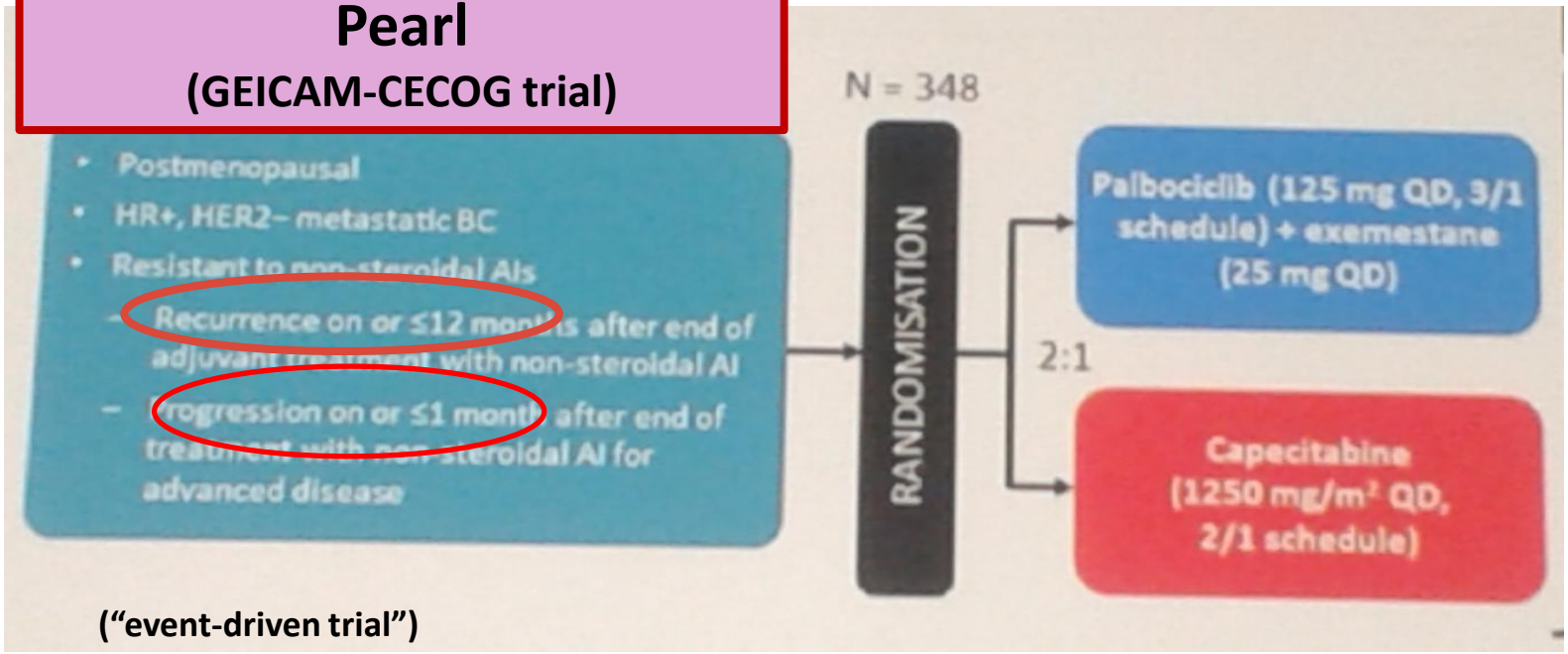
August, 2015

PALOMA -2 (1008)



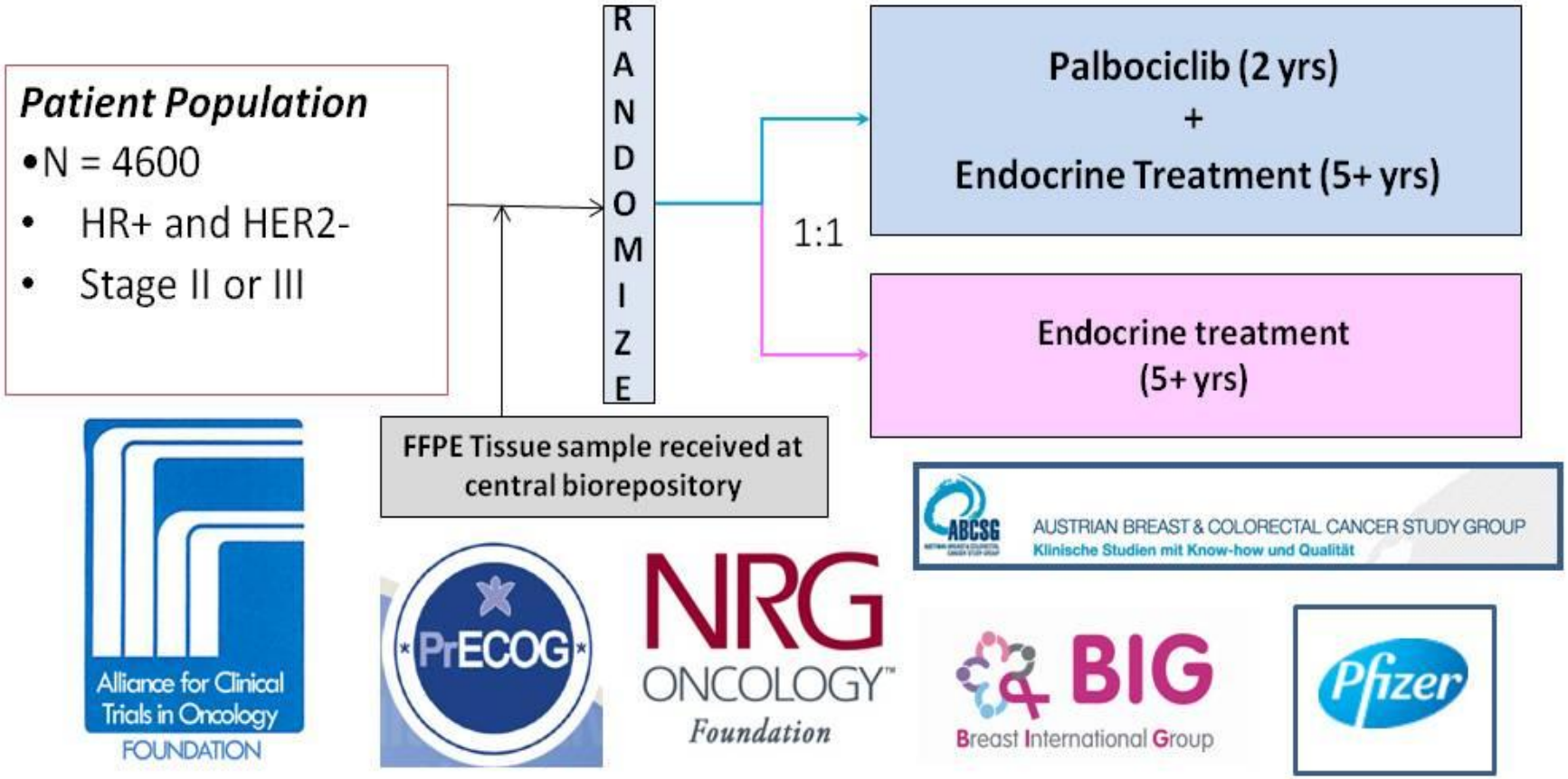
(Completed enrollment)

Pearl
(GEICAM-CECOG trial)



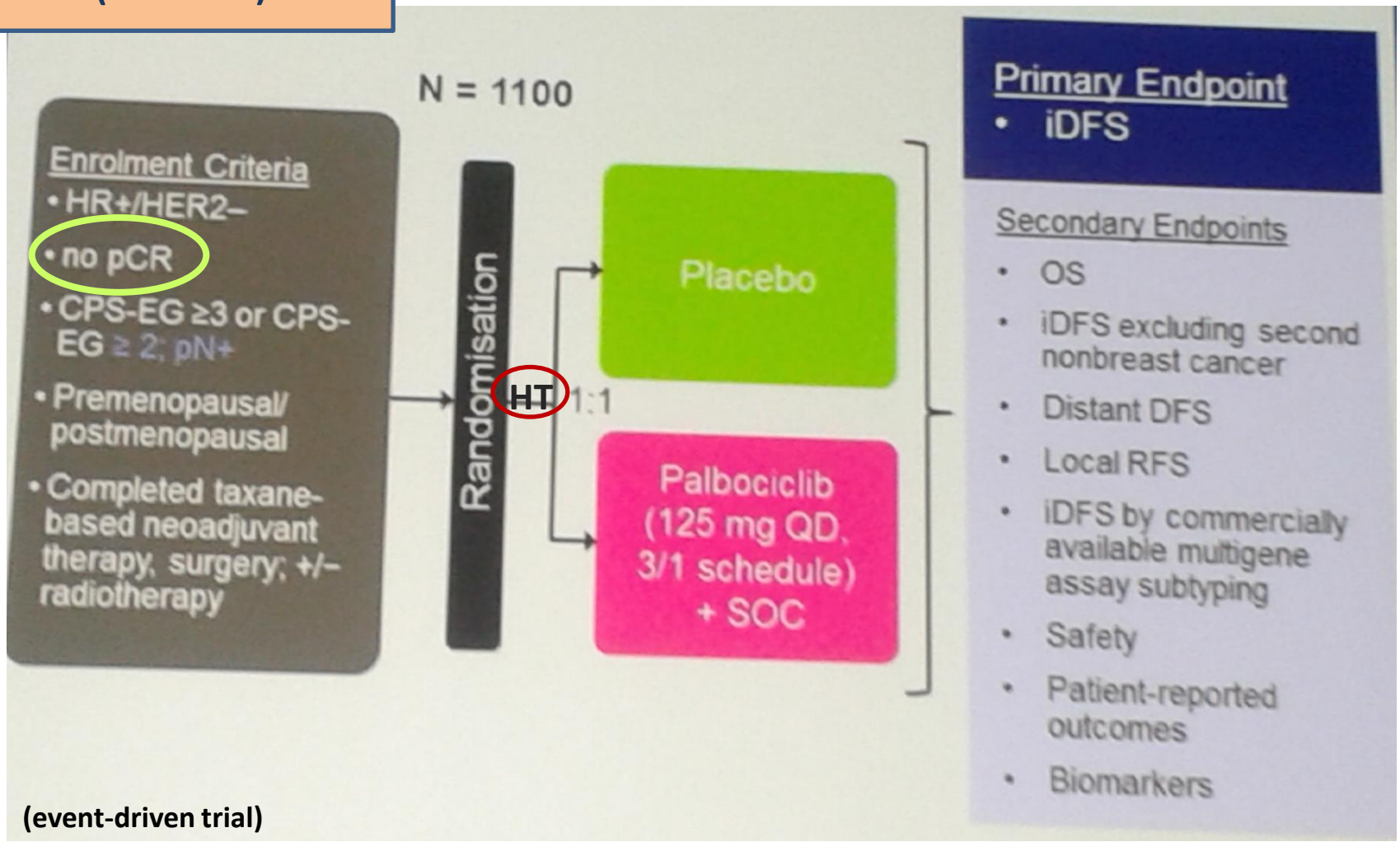
("event-driven trial")

PALbociclib CoLlaborative Adjuvant Study (PALLAS)



Presented By Joseph Sparano at 2015 ASCO Annual Meeting

PENELOPE-B
(GBG trial)

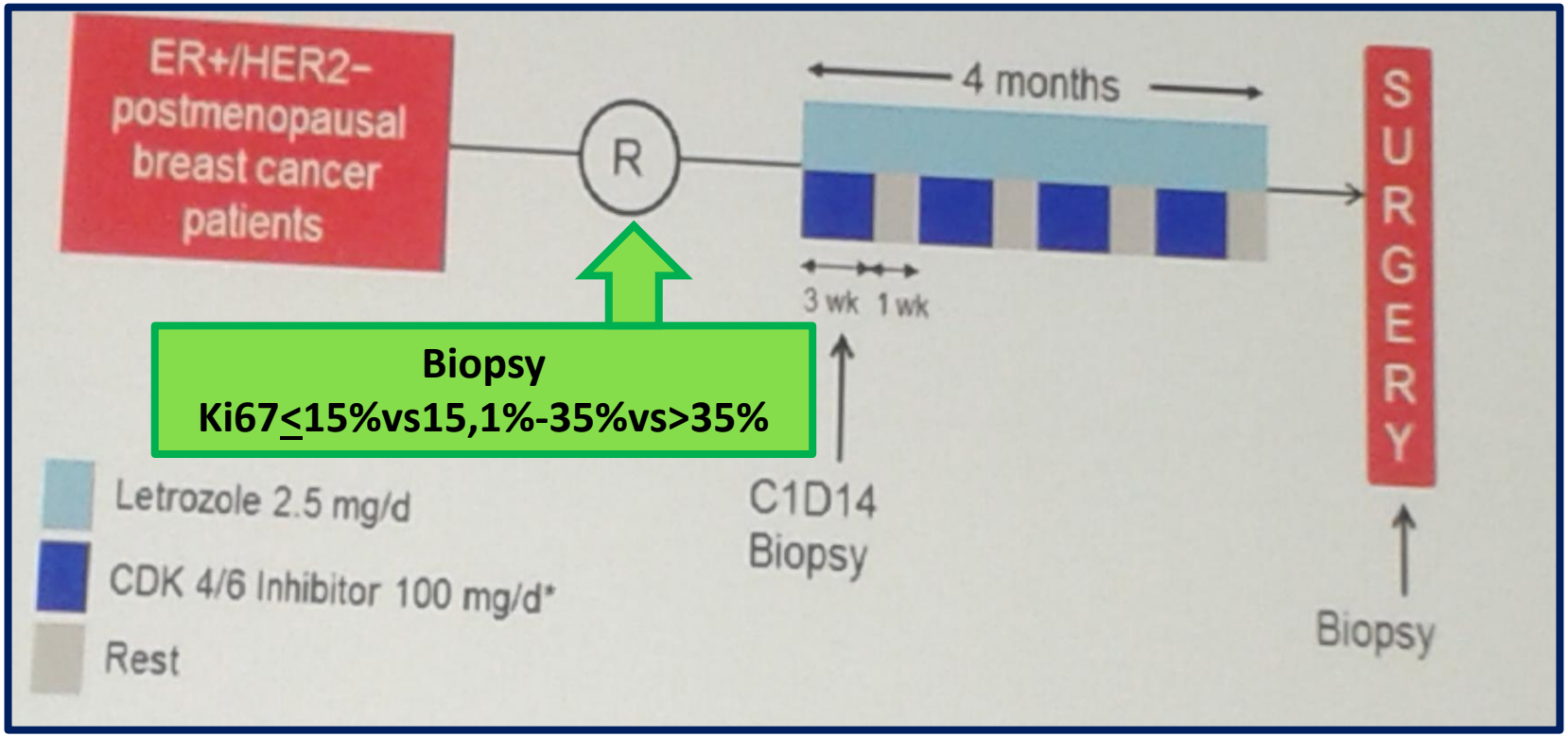


(event-driven trial)

Von Minckwitz G et al, SABCS; December 10-14 2013

Neoadjuvant Palbociclib Plus Letrozole

Design: Open-label, multicentre, single-arm pilot study to determine efficacy and safety of neoadjuvant palbociclib plus letrozole in 3 of 4 weeks cycles for 4 months

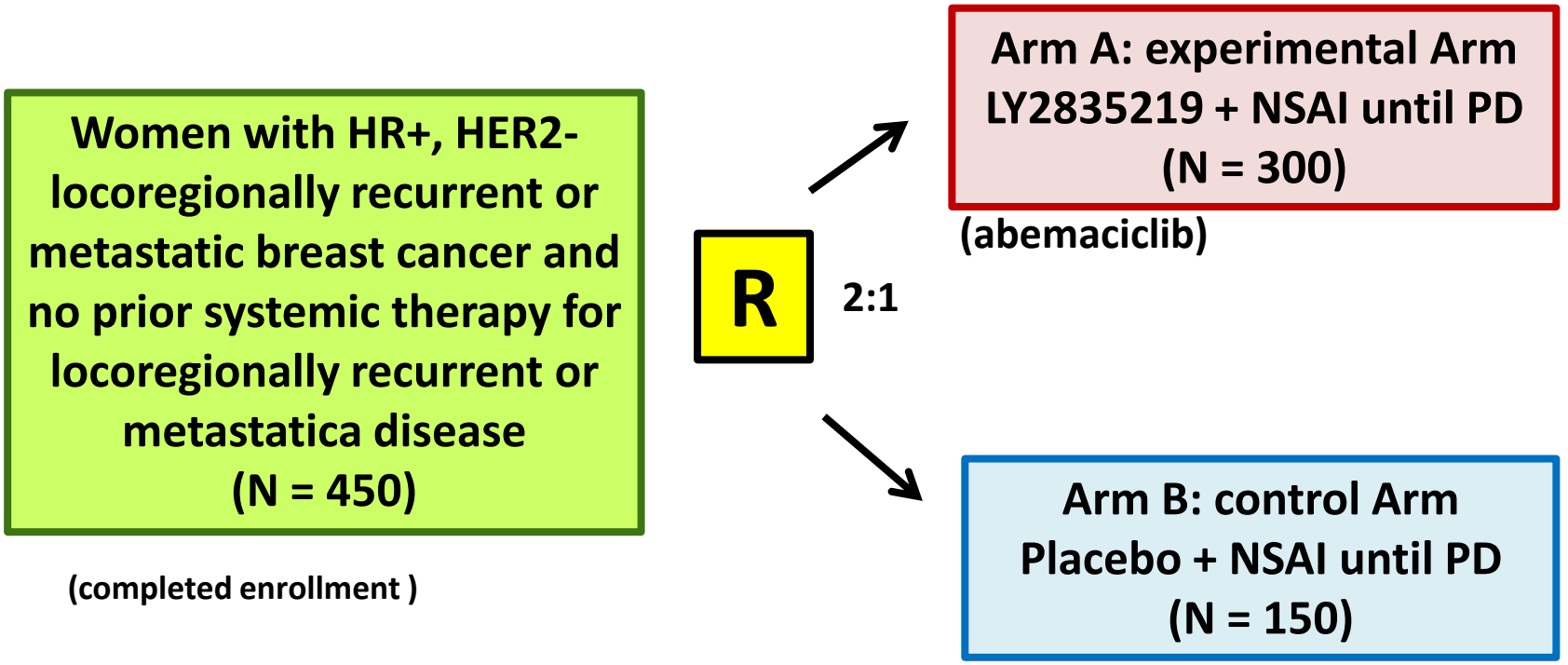


Patients will be given letrozole 2.5 mg/d plus PD0332991 (CDK 4/6 inhibitors) 125 mg/d for 3 out of 4 weeks in repeated cycles for 16 weeks (4 cycles) before surgery

Chrow LWC et al, SABCS; December 9-13 2014, **(GBG trial)**

13Y-MC-JPBM Clinical Protocol (Monarch Study)

A randomized double-blind, placebo-controlled, phase 3 study on nonsteroidal aromatase inhibitors (anastrozole or letrozole) plus LY2835219, a CDK4/6 inhibitor or placebo in postmenopausal women with hormone receptor-positive, HER2-negative locoregionally recurrent or metastatic breast cancer without no prior systemic therapy in this disease setting



Experimental Arm A: LY2835219 150 mg orally twice/d on day 1 to 28 +
non-steroidal aromatase inhibitor once/d of a 28-day cycle

Control Arm B: Placebo orally twice/day on day 1 to 28 +
non-steroidal aromatase inhibitor once/d of a 28-day cycle

WHAT DO WE LEARN UNTILL NOW:

- Endocrine-directed therapy for women with metastatic HR+, HER2-negative breast cancer remains the treatment of choice
- Recurrence or resistance on endocrine therapy remains a major problem in HR+ breast cancer
- Therapies that extend benefit of endocrine therapy (anti mTOR-everolimus, anti CD4/6-palbociclib) address key endocrine intracellular tumor growth and cell signaling pathways ("target" molecular therapy)

  → delays disease progression and the need to transition to cytotoxic agents

A NEW «TARGET THERAPY» IN ENDOCRINE-RESPONSIVE BREAST CANCER OTHERWISE THE «HORMONAL RECEPTORS»

Always address eligible patients to clinical trials

WHAT DO WE LEARN UNTILL NOW:

- 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.

WHAT DO WE LEARN UNTILL NOW:

Patients believe “ORAL”=“NON TOXIC”

- Many of drugs used to treat patients with HR+/HER2- breast cancers are orally administred

- More physician time is required to educate patients about adverse events and to emphasize adherence and self-monitoring

- Frequent monitoring visits are needed (i.e. 4 weeks)

- Nurses need more education to be able to counsel patients and to allert physician to early signs of side effects treatment-related

SIDE EFFECTS IN BOLERO -2 STUDY :

anti mTOR «everolimus»+ steroidal aromatase inhibitor «exemestane»

- Higher incidence of adverse events with combination exemestane/everolimus
  - Predictable
  - Easily managed with dose reductions and interruptions

Adverse Event	Grade 3/4	Proportion Resolved	Median Time to Resolution (Weeks; 95% CI)
Stomatitis	8.1%	97%	3.1; 1.9 - 5.3
Fatigue	6.6%	72%	8.0; 2.7 - 18.7
Pneumonitis (noninfectious)	4.1%	80%	3.8; 1.3 - 7.1
Hyperglycemia and new diabetes	5.8%	46%	29.1; 10.1 - NA
Hyperlipidemia	0.8%	25%	NA; 19.3 - NA
Infections/infestations	6.6%	84%	3.0; 1.0 - 18.0

Rugo HS, et al. *Ann Oncol*. 2014;25:808-815.[5]

Paloma-1 Study: SIDE EFFECTS

	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%

PALOMA-3 Study: SIDE EFFFECTS

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 (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 reduction (21%) and interruption (45%)

Presented By Nicholas Turner at 2015 ASCO Annual Meeting

CDK1-2-5-9 inhibitor (DINACICLIB) (2)

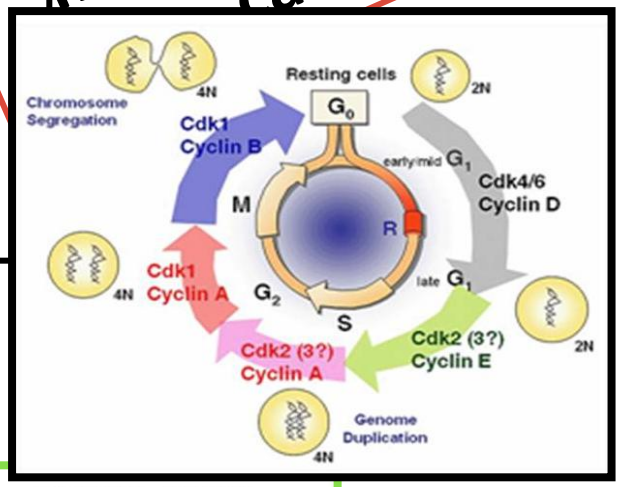
R
- capecitabine — 4 PR
- dinaciclib 50mg/sqm iv q3wks — 2 PR

N = 30

Targeting therapy in metastatic breast cancer

CDKi — CDKs
- PD 0332991 Phase II CDK4/6
- Dinaciclib Phase I CDK1/2/5/9
- Seliciclib Phase I CDK2/7/9

~~Evading growth suppressors~~



In BRCA-mutated breast cancer (genomic instability)

- Olaparib Phase III
- Veliparib Phase III
- ~~Iniparib Phase III~~
- CO-338 Phase II
- INO-1001 Phase II
- MK-4827 Phase II
- E7016 Phase I
- BMN-673 Phase I
- CEP-9722 Phase I

CDK1 inhibition in the context of MYC amplification
(D. Horiuchi et al, J of Exp Med 2012)

CDK1 inhibition + PARP inhibitor
(G. Shapiro, Dana Farber)

CDK inhibitor + **PARPs inhibitor**

New hopes for triple negative B.C. ?

Metzer-Filho, JCO 2012