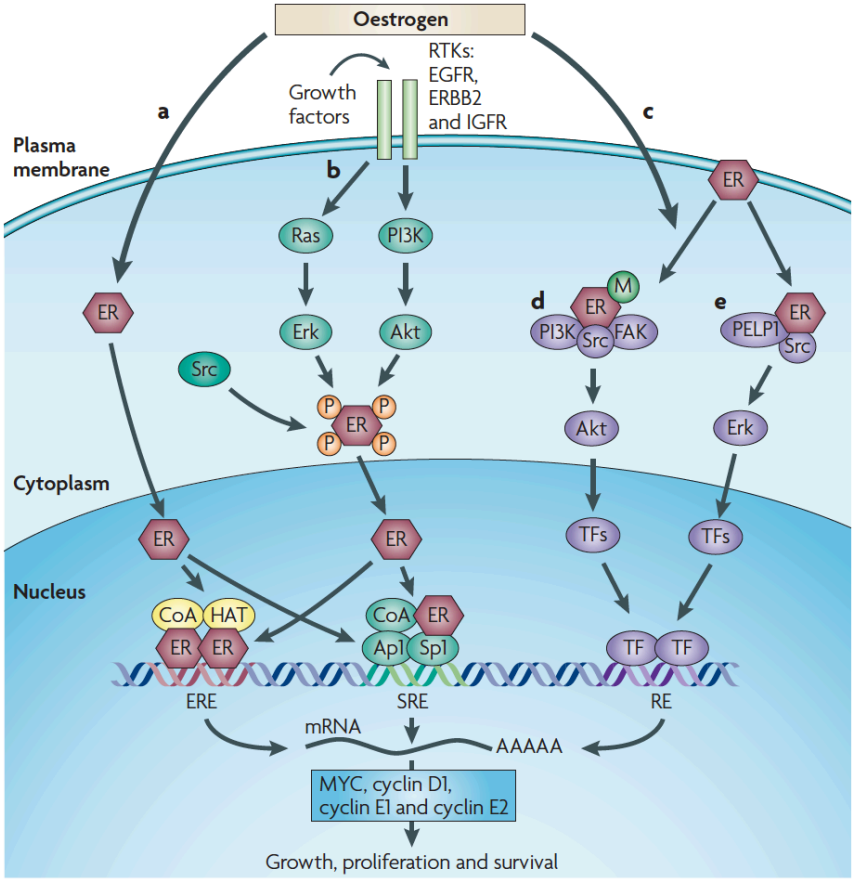
CDK 4 / 6 Inhibitoren

Georg Pfeiler

Estrogen Action

NATURE REVIEWS | CANCER

Musgrove&Sutherland 2009



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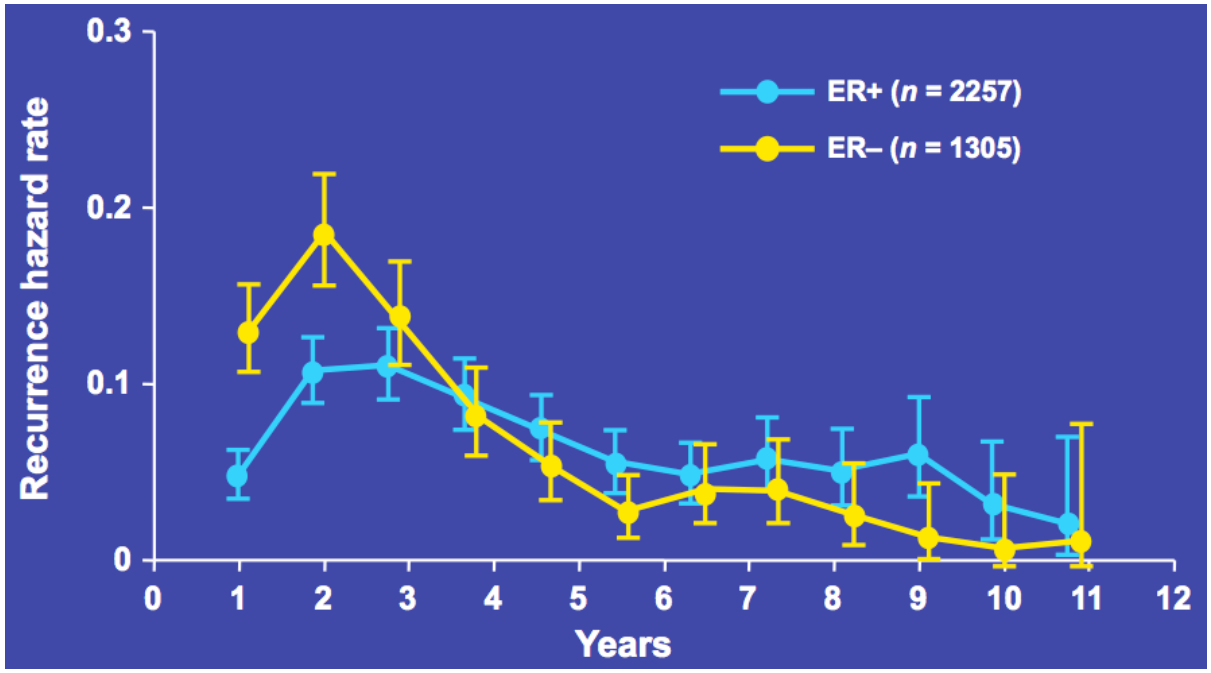
Clinical Predictors of Resistance

- Her2 amplification
- Lower E2 expression
- Disease Free intervall
- Duration of response
- Prior Treatment
- BMI?? ☺

Clinical Predictors of Resistance



Saphner *et al. J Clin Oncol* 1996;14:2738–46

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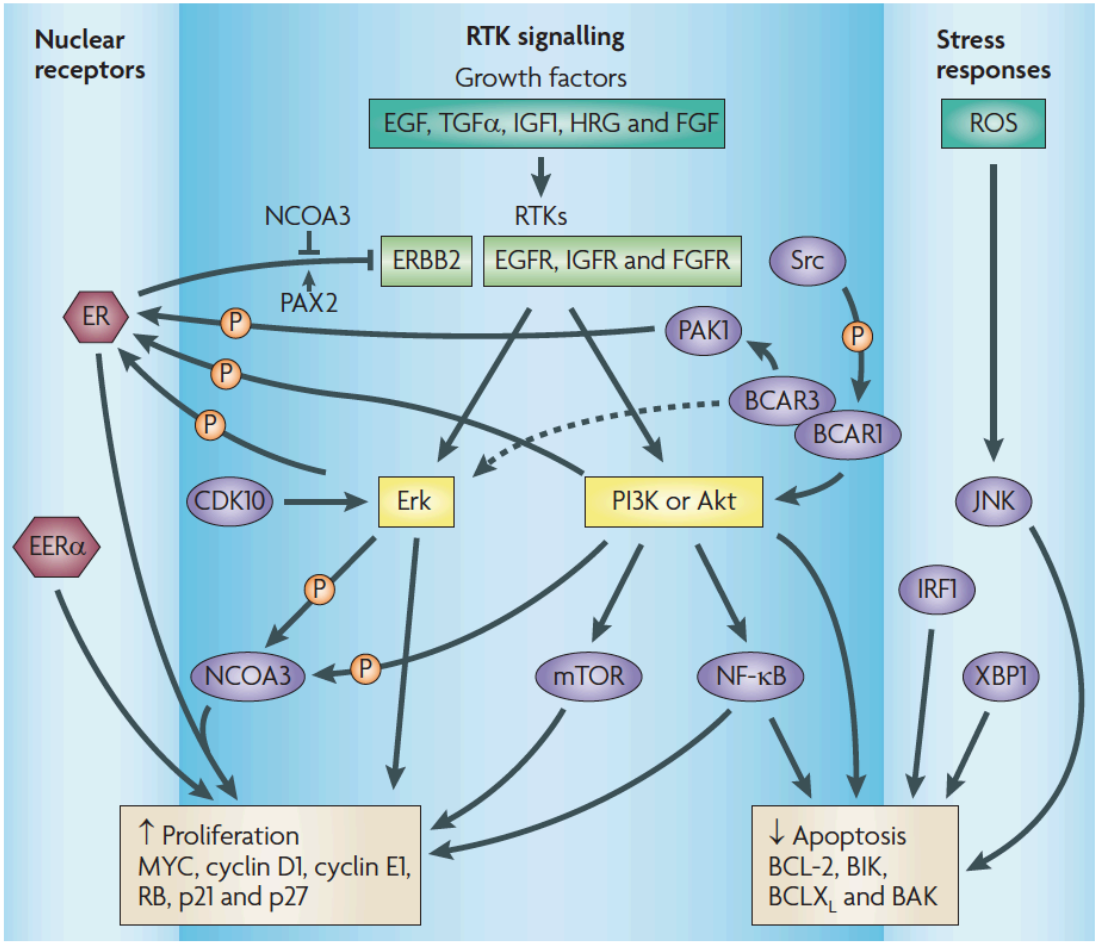
Endocrine Resistance

NATURE REVIEWS | CANCER

Musgrove&Sutherland 2009



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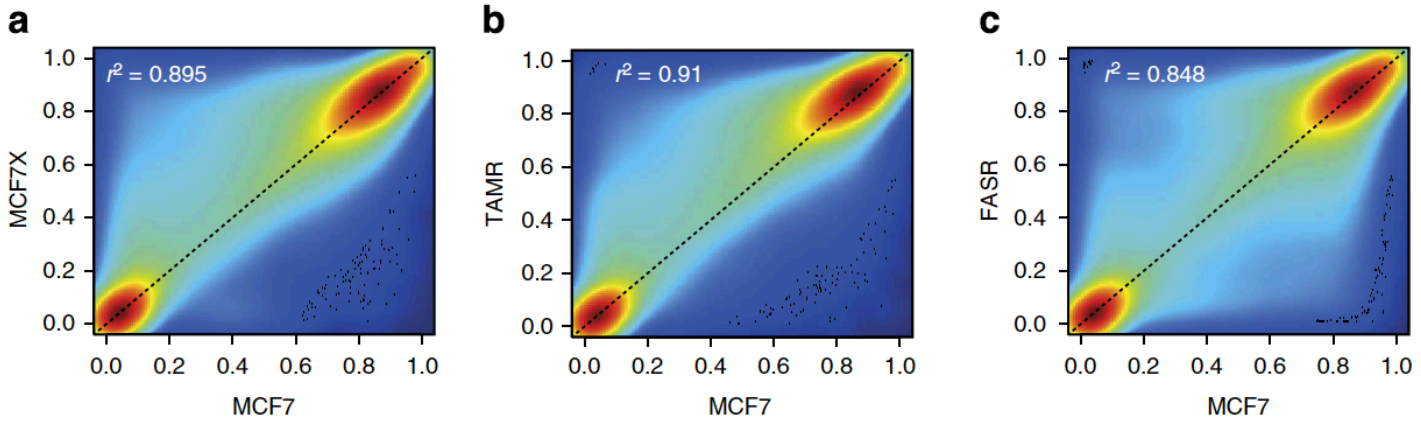
ARTICLE

Received 18 Mar 2015 | Accepted 6 Jun 2015 | Published 14 Jul 2015

DOI: 10.1038/ncomms8758 OPEN

DNA methylation of oestrogen-regulated enhancers defines endocrine sensitivity in breast cancer

Andrew Stone[1,2,*], Elena Zotenko[1,2,*], Warwick J. Locke[1,2], Darren Korbie[3], Ewan K.A. Millar[4,5,6,7], Ruth Pidsley[1,2], Clare Stirzaker[1,2], Peter Graham[7,8], Matt Trau[3], Elizabeth A. Musgrove[2,4,9], Robert I. Nicholson[10], Julia M.W. Gee[10] & Susan J. Clark[1,2]



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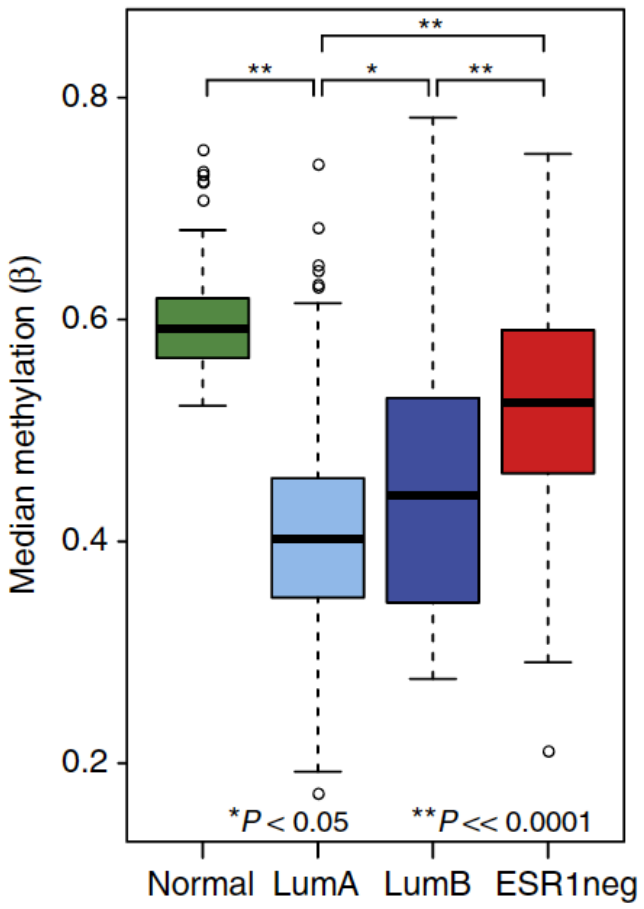

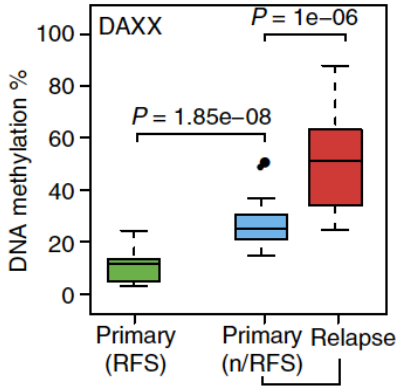

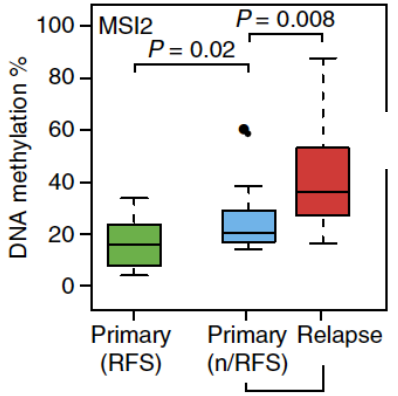

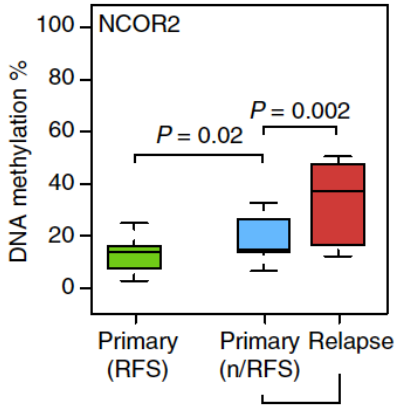

NATURE COMMUNICATIONS

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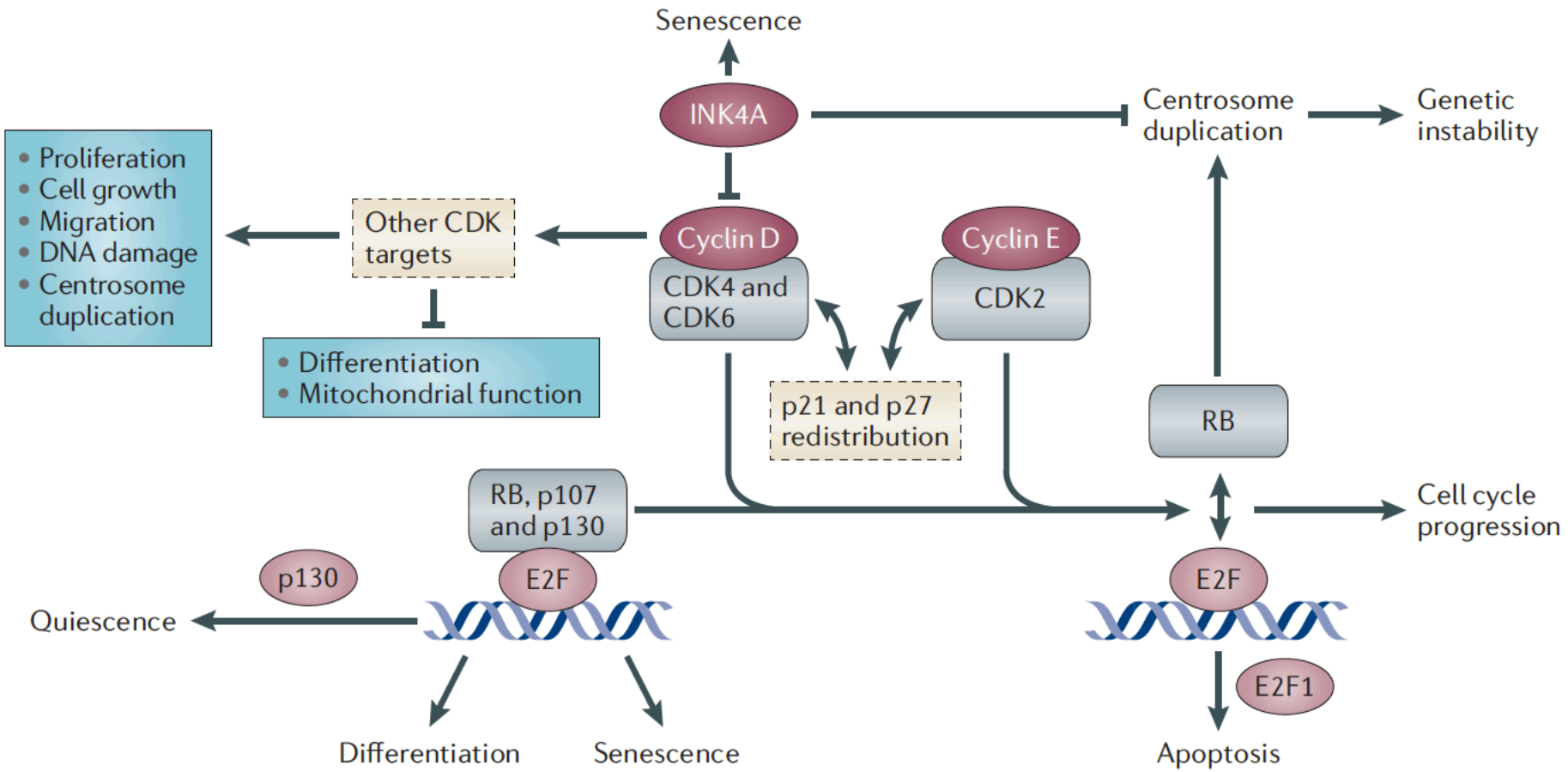
CDK-dependent functions of cyclin D



Musgrove et al. 2011

NATURE REVIEWS | CANCER

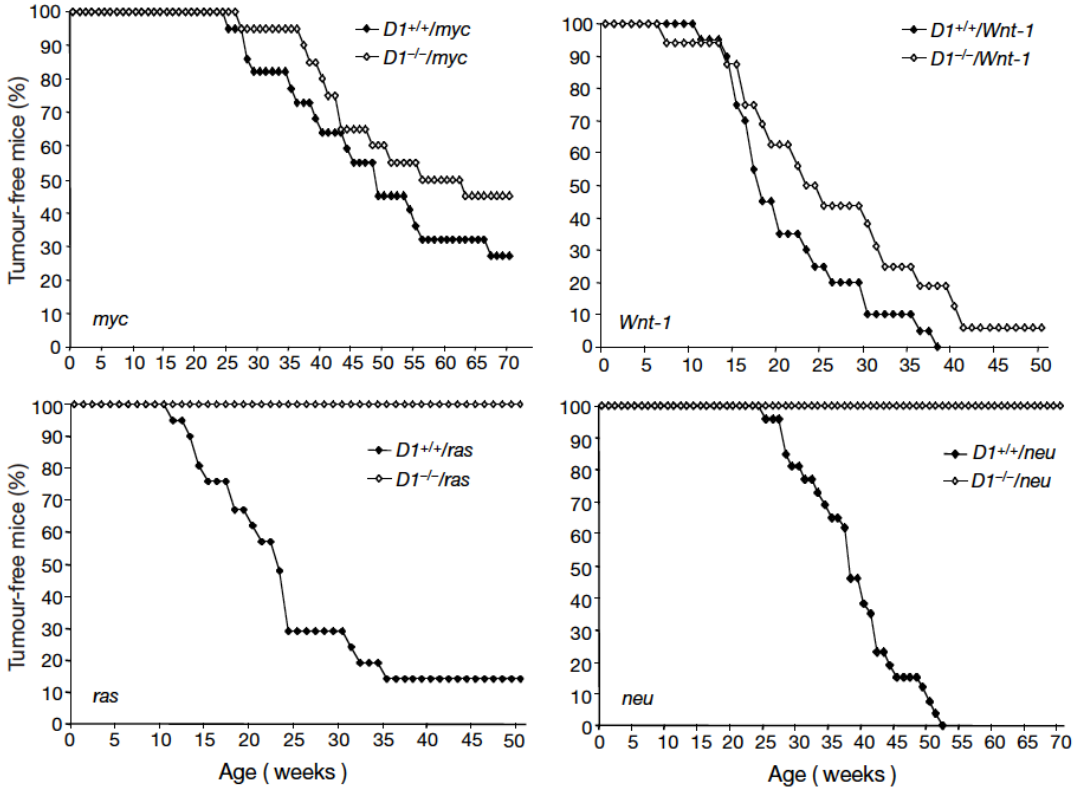
Non-catalytic / CDK 4-6 independent effects of Cyclin D1

- Migration
- DNA damage response (BRCA2, Rad51)
- Cell cycle progression (ER, SRC1)
- Differentiation (HDACs)

Specific protection against breast cancers by cyclin D1 ablation

NATURE | VOL 411 | 28 JUNE 2001

Qunyan Yu, Yan Geng & Piotr Sicinski



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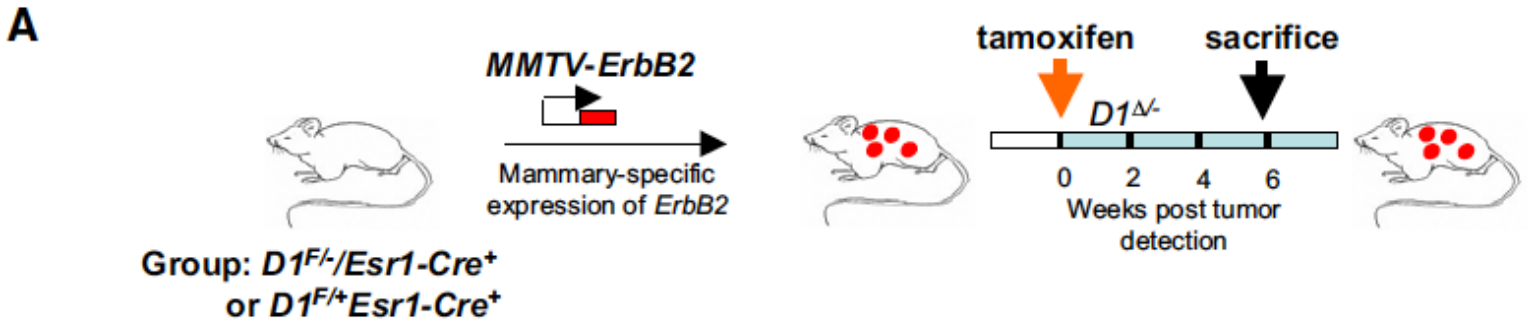
The Requirement for Cyclin D Function in Tumor Maintenance

Cancer Cell
Article

Yoon Jong Choi,[1,8,11] Xiaoyu Li,[2,9,11] Per Hydbring,[1,8] Takaomi Sanda,[3,7,10] Joanna Stefano,[1] Amanda L. Christie,[4] Sabina Signoretti,[5,6] A. Thomas Look,[3,7,10] Andrew L. Kung,[4,10,12] Harald von Boehmer,[2,9] and Piotr Sicinski[1,8,*]

Cancer Cell *22*, 438–451, October 16, 2012



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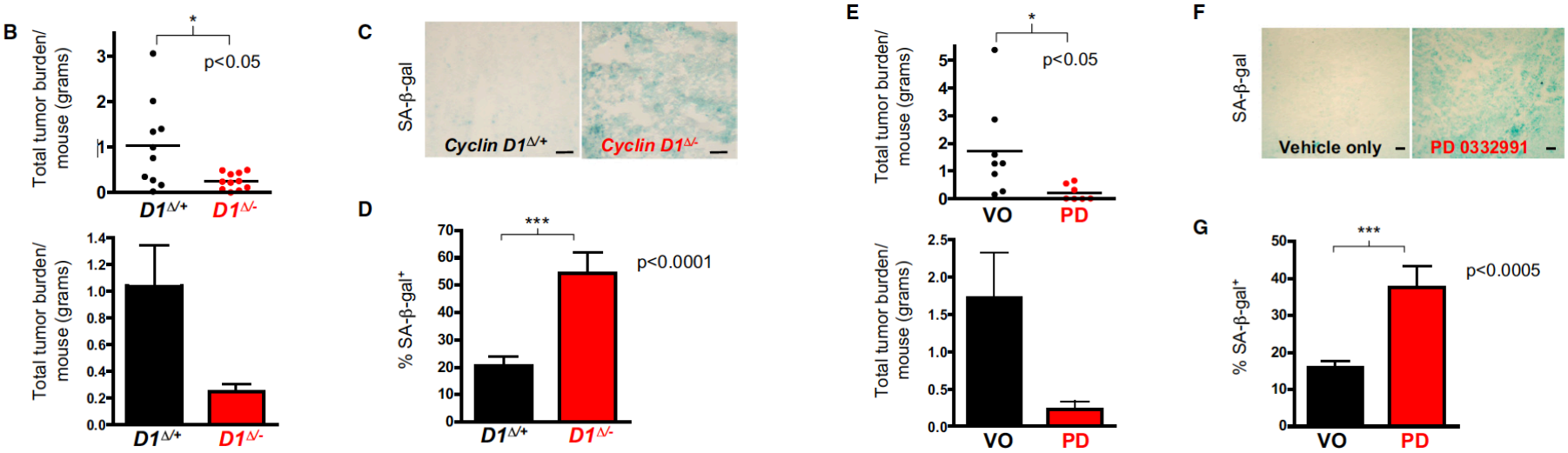


Georg Pfeiler

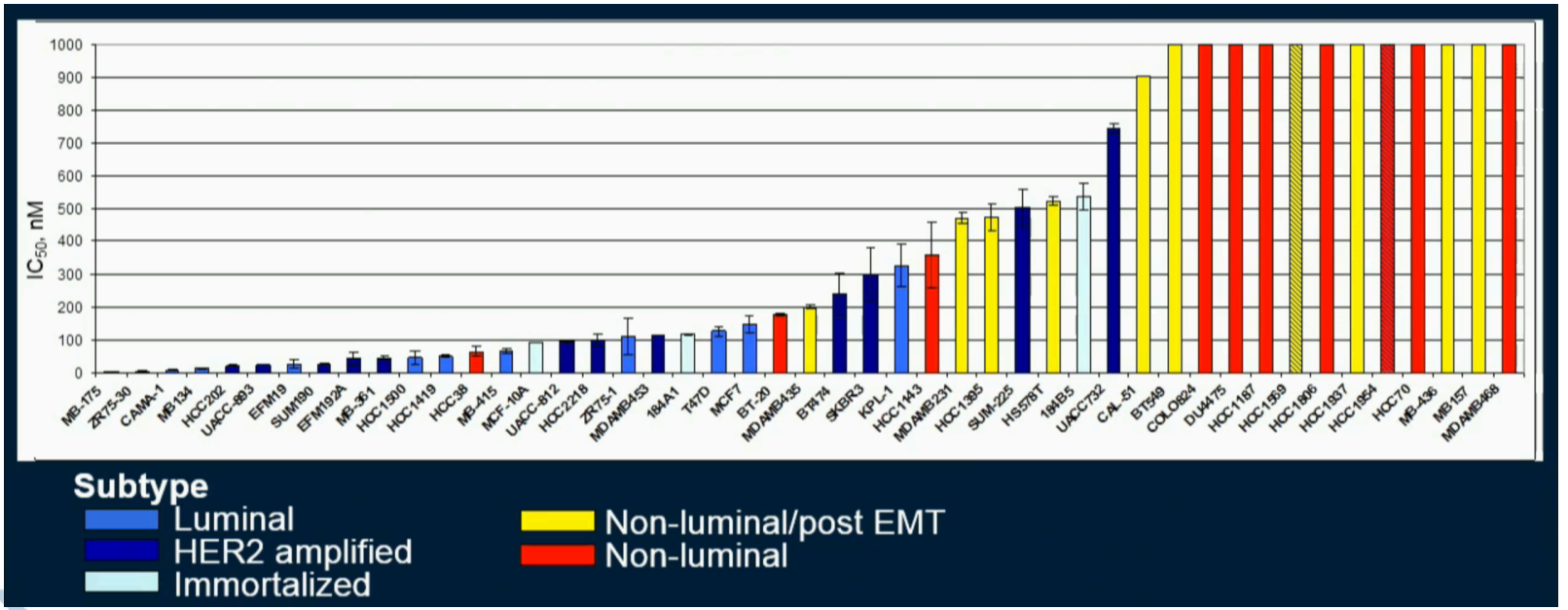
Research article

Open Access

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]

Breast Cancer Research 2009, 11:R77



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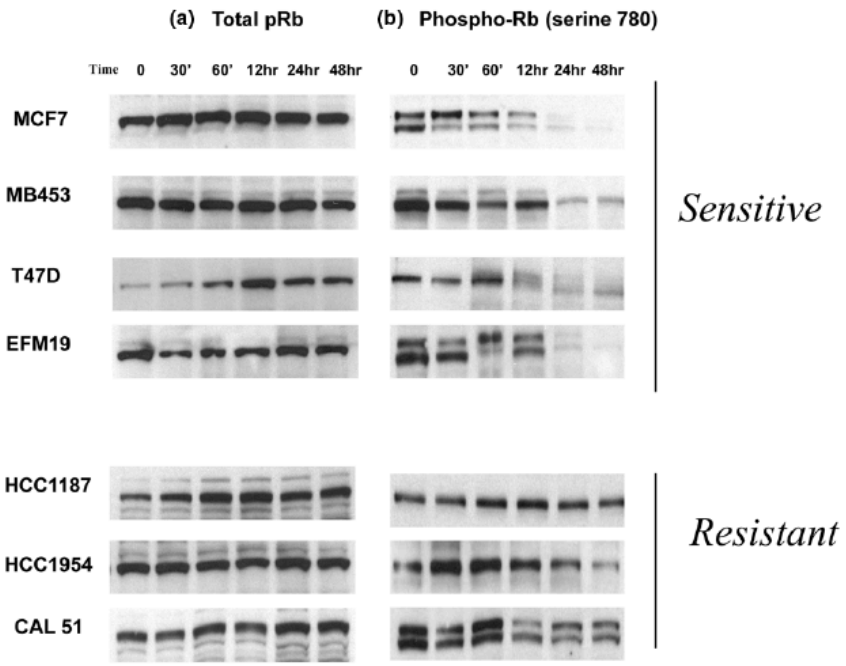

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Primary resistance

- Rb-negativity
- Lack of co-deletion of CDKN2A/CDKN2C in glioblastoma

Cell line	RB alteration class	% senescence	Colonies/100000 cells
LN-319	No alteration	0%	confluent
LN-235	RB del	0%	confluent
LN-Z308	CDK4 amp	0%	confluent
Hs683	CDKN2A del	19.5 ± 3.5%	>500
LN-18	CDKN2A del	0.65 ± 0.2%	>1000
LN-443	CDKN2A del	0%	confluent
T98G	CDKN2A/CDKN2C del	0.75 ± 0.2%	confluent
LN-229	CDKN2A/CDKN2C del	>90%	7 ± 2
U87MG	CDKN2A/CDKN2C del	50%	89 ± 2
A1207	CDKN2A/CDKN2C del	>90%	9 ± 2

Wiedermeyer et al. PNAS 2010; 107: 11501-6

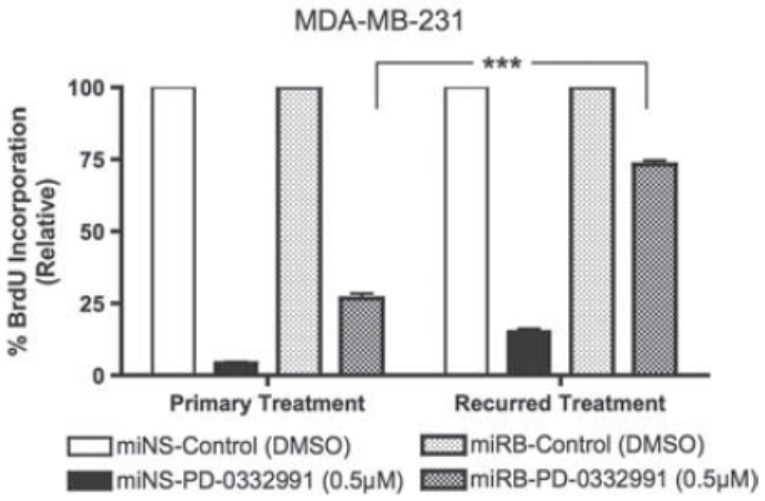
Acquired resistance

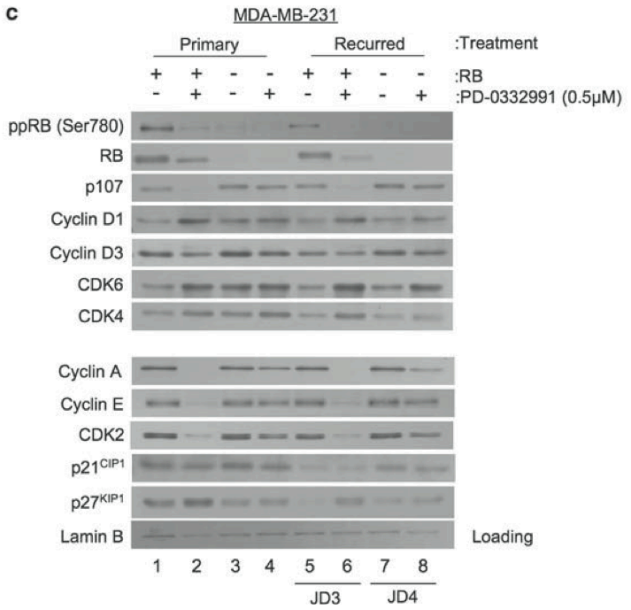
Oncogene (2010) 29, 4018–4032

ORIGINAL ARTICLE

Therapeutic CDK4/6 inhibition in breast cancer: key mechanisms of response and failure

JL Dean[1,2], C Thangavel[1,2], AK McClendon[1,2], CA Reed[1,2] and ES Knudsen[1,2]





Reduced $p27^{Kip1}$ activates CDK2 and promotes Rb phosphorylation and reversal of G1 arrest

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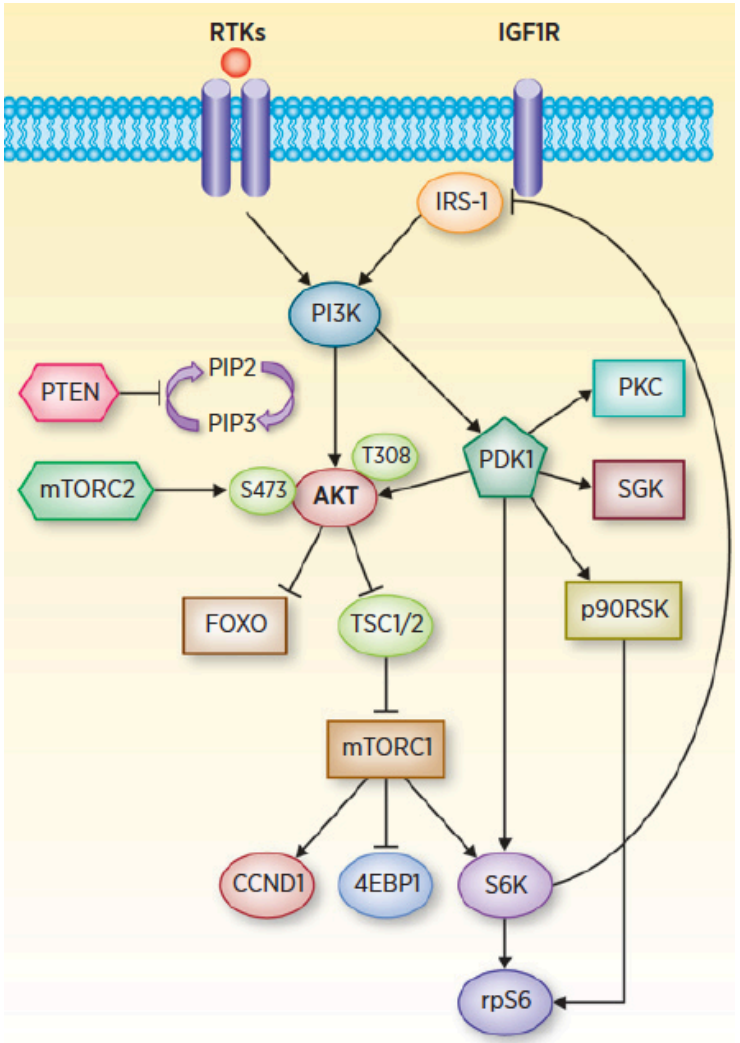
Resistance through PDK1



Valerie M. Jansen, Ingrid A. Mayer, and Carlos L. Arteaga

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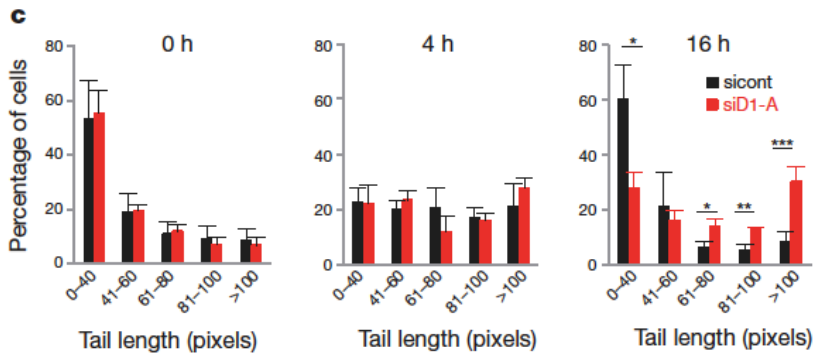
A function for cyclin D1 in DNA repair uncovered by protein interactome analyses in human cancers

Siwanon Jirawatnotai[1,2], Yiduo Hu[1]*, Wojciech Michowski[1]*, Joshua E. Elias[3]†, Lisa Becks[1,4], Frederic Bienvenu[1]†, Agnieszka Zagozdzon[1], Tapasree Goswami[3], Yaoyu E. Wang[5], Alan B. Clark[6], Thomas A. Kunkel[6], Tanja van Harn[1], Bing Xia[7], Mick Correll[5], John Quackenbush[5,8], David M. Livingston[1], Steven P. Gygi[3] & Piotr Sicinski[1]

NATURE | VOL 474 | 9 JUNE 2011



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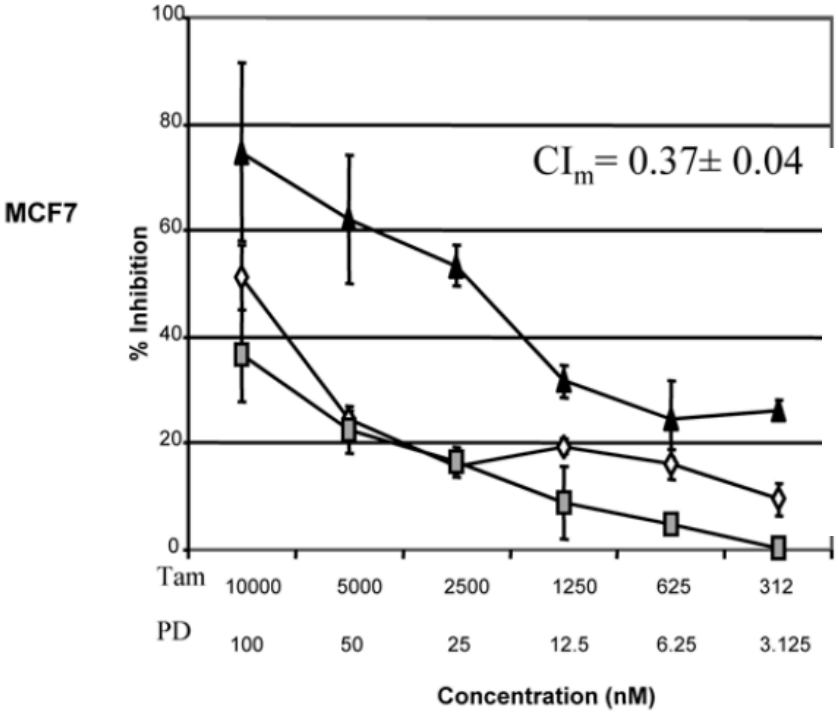
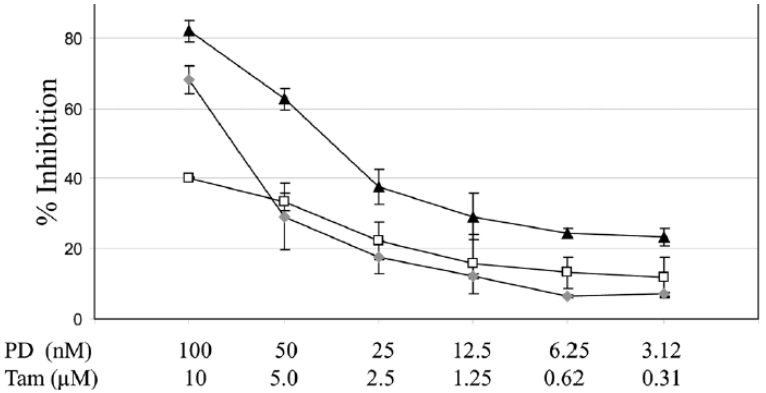
Synergistic effects





Breast Cancer Research 2009,

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

that accrued sequentially: in cohort 1, patients were enrolled on the basis of their oestrogen receptor-positive and HER2-negative biomarker status alone, whereas in cohort 2 they were also required to have cancers with amplification of cyclin D1 (*CCND1*), loss of p16 (also known as INK4A or CDKN2A), or both. All patients were

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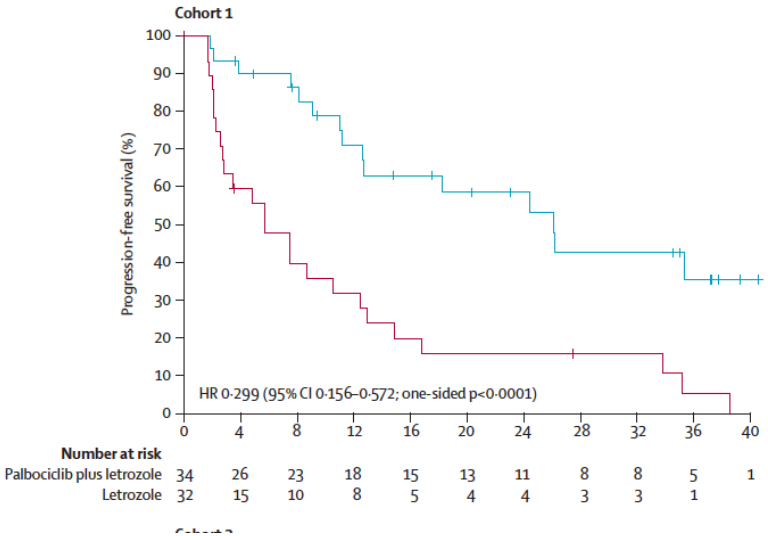

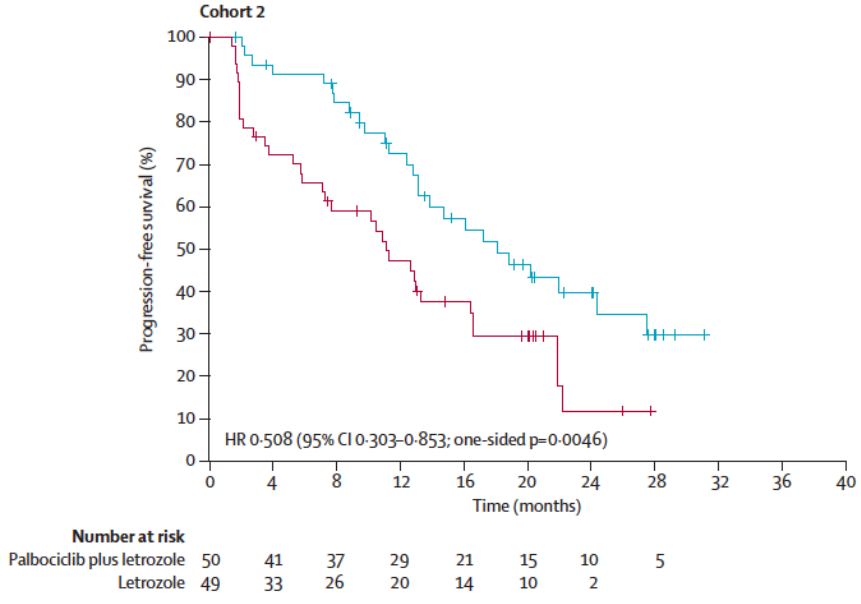

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PALOMA-2: Primary Results From a Phase 3 Trial of Palbociclib Plus Letrozole Compared With Placebo Plus Letrozole in Postmenopausal Women With ER+/HER2– Advanced Breast Cancer

Richard S. Finn,[1] Miguel Martin,[2] Hope S. Rugo,[3] Stephen Jones,[4] Seock-Ah Im,[5] Karen Gelmon,[6] Nadia Harbeck,[7] Oleg N. Lipatov,[8] Janice M. Walshe,[9] Stacy Moulder,[10] Eric Gauthier,[11] Dongrui R. Lu,[11] Sophia Randolph,[11] Veronique Dieras,[12] Dennis J. Slamon[1]

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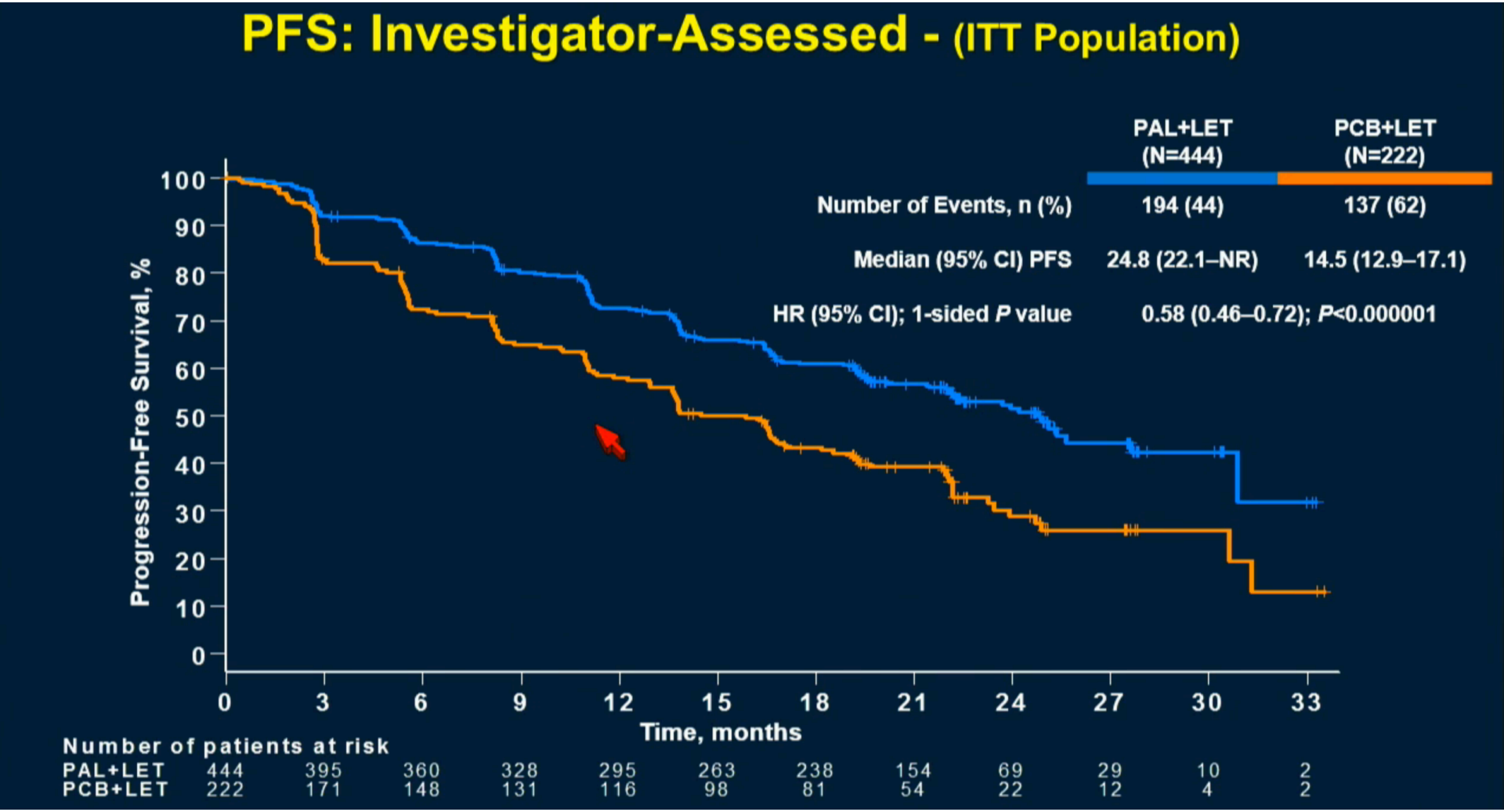
PFS: Investigator-Assessed - (ITT Population)



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PFS Subgroup Analysis (ITT, Investigator Assessment)

Subgroup		n (%)	Hazard Ratio (95% CI)
All randomized patients		666 (100)	0.576 (0.463–0.718)
Age	<65 y	404 (60.7)	0.567 (0.434–0.740)
	≥65 y	262 (39.3)	0.571 (0.386–0.843)
Race	White	516 (77.5)	0.576 (0.450–0.739)
	Asian	95 (14.3)	0.484 (0.269–0.871)
Site of metastatic disease	Visceral	324 (48.6)	0.633 (0.472–0.849)
	Nonvisceral	342 (51.4)	0.502 (0.360–0.699)
Prior hormonal therapy	Yes	375 (56.3)	0.528 (0.400–0.698)
	No	291 (43.7)	0.628 (0.439, 0.897)
Disease-free interval	De novo metastases	248 (37.2)	0.674 (0.457–0.993)
	≤12 mo	147 (22.1)	0.501 (0.329–0.761)
	>12 mo	271 (40.7)	0.516 (0.365–0.731)
Region	North America	267 (40.1)	0.605 (0.431–0.849)
	Europe	307 (46.1)	0.571 (0.410–0.796)
	Asia/Pacific	92 (13.8)	0.486 (0.270, 0.872)
ECOG performance status	0	359 (53.9)	0.646 (0.466–0.896)
	1/2	307 (46.1)	0.531 (0.393–0.718)
Bone-only disease at baseline	Yes	151 (22.7)	0.363 (0.221–0.594)
	No	515 (77.3)	0.654 (0.512–0.837)
Measurable disease	Yes	509 (76.4)	0.663 (0.517–0.849)
	No	157 (23.6)	0.350 (0.215–0.568)
Prior chemotherapy	Yes	322 (48.3)	0.533 (0.395–0.720)
	No	344 (51.7)	0.611 (0.443–0.842)
Most recent therapy	Aromatase inhibitor	135 (20.3)	0.549 (0.341–0.883)
	Antiestrogen	229 (34.4)	0.558 (0.390–0.799)
Number of disease sites	1	204 (30.6)	0.511 (0.339–0.770)
	≥2	462 (69.4)	0.606 (0.467–0.787)

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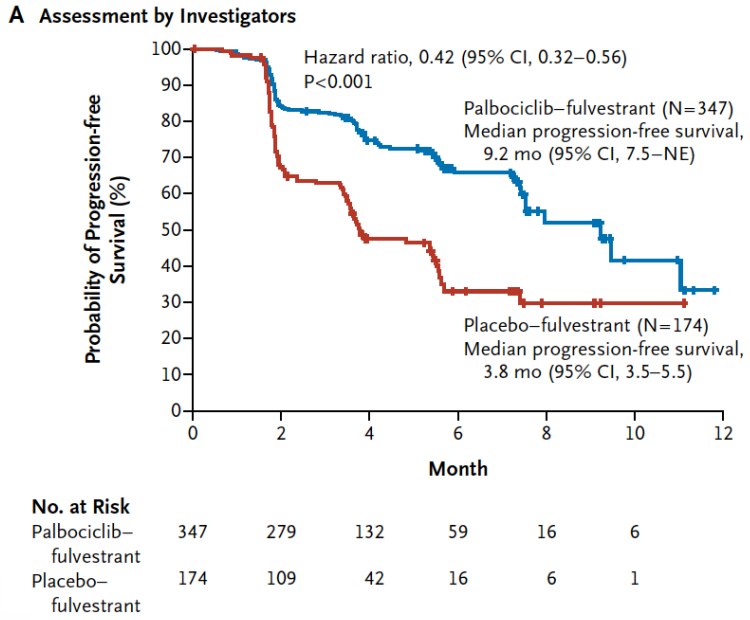
Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer

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.

N ENGL J MED 373;3 NEJM.ORG JULY 16, 2015



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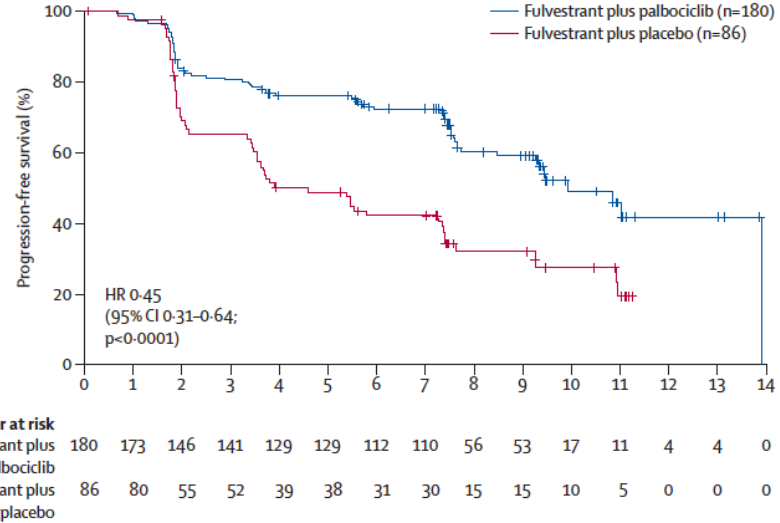
Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial

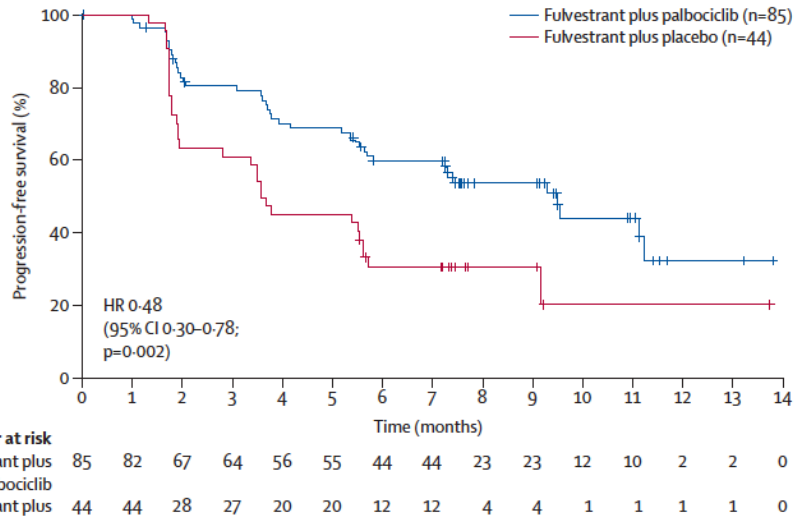
Lancet Oncol 2016; 17: 425–39

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*

No PI3K mutation



PI3K mutation



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COMPREHENSIVE CANCER CENTER VIENNA

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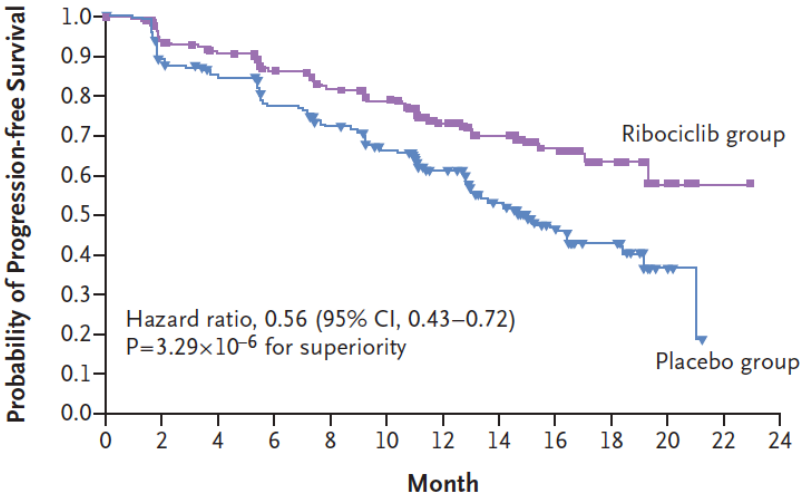
Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer

G.N. Hortobagyi, S.M. Stemmer, H.A. Burris, Y.-S. Yap, G.S. Sonke,

N ENGL J MED 375;18 NEJM.ORG NOVEMBER 3, 2016



No. at Risk

Ribociclib	334	294	277	257	240	226	164	119	68	20	6	1	0
Placebo	334	279	264	237	217	192	143	88	44	23	5	0	0

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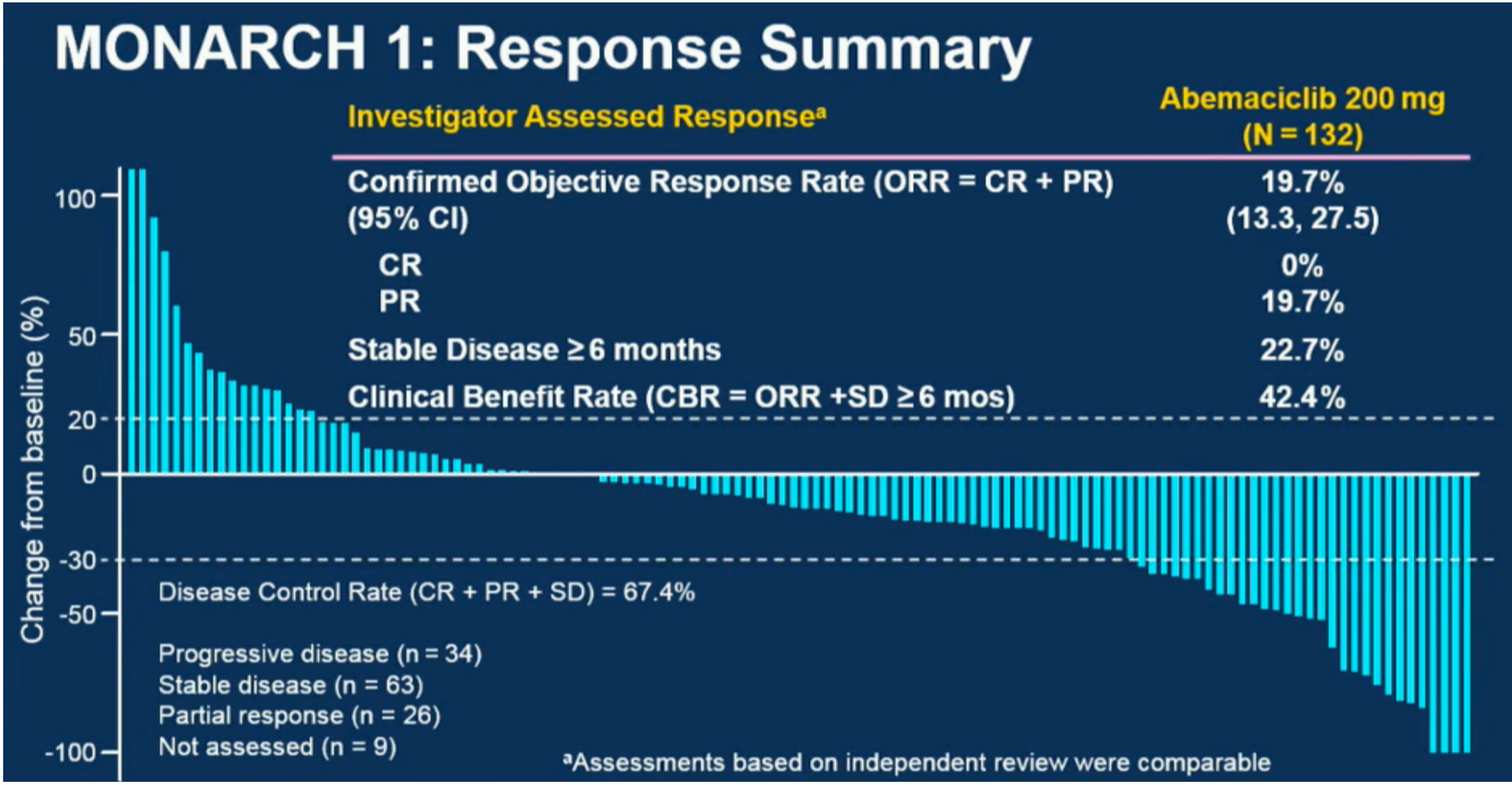
MONARCH 1: Response Summary



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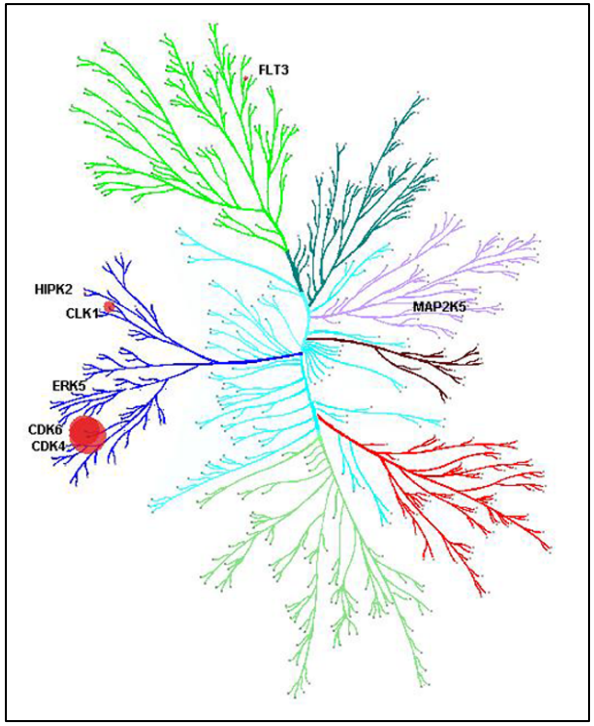
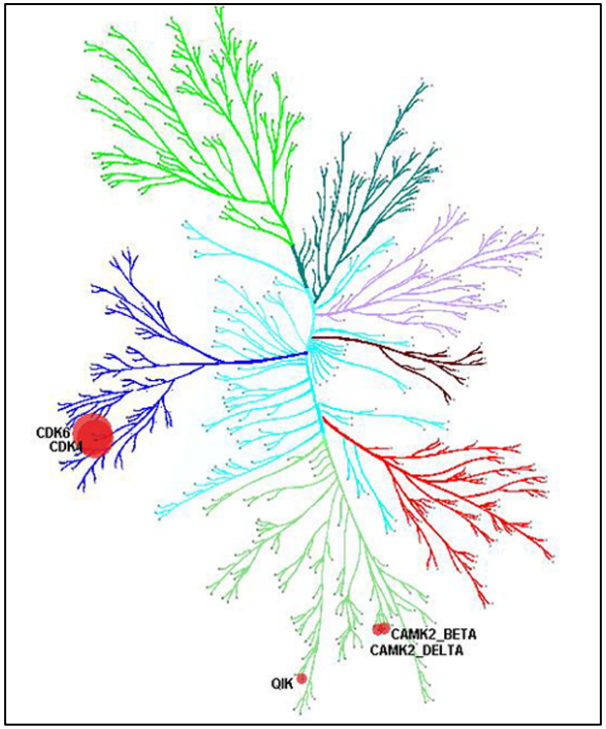
Target Profiles of CDK4/6 Inhibitors in Tumor Cell Assays

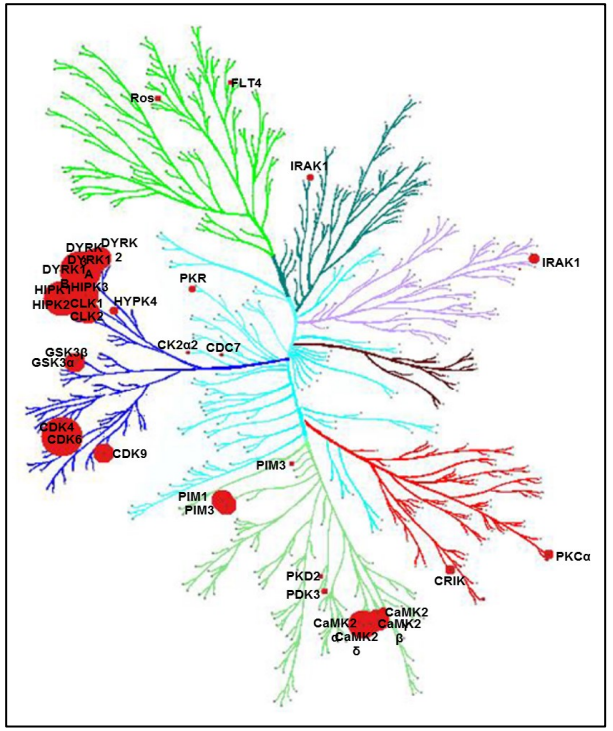
Palbociclib



Ribociclib



Abemaciclib



Selectivity

- 1x
- 10x
- 100x

NSAF, normalized spectral abundance factor.
Chen P, et al. *Molec Cancer Ther*. 2016.

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Metabolism and Pharmacokinetics

	Palbociclib[1]	Ribociclib[2-6]	Abemaciclib[7-12]
Plasma ½ life	**29 (± 5) hours**	**32.0 (8.06- 97.9) hours**	**20.5 hours**
Median T_{max}	6-12 hours	2.4 (0.683-7.82) hours	4-6 hours
Plasma accumulation	Median accumulation ratio = 2.4 (range, 1.5-4.2) with daily dosing	Accumulation ratio = 2.51 (range, 0.97-6.40) with daily dosing	Plasma concentrations increased with dose following a single dose between 50 and 275 mg
Metabolic routes	Hepatic metabolism; no effect of mild hepatic or mild-moderate renal impairment on palbociclib exposure; not studied in patients with moderate-severe hepatic or severe renal impairment	Hepatic metabolism; no effect of mild hepatic impairment; ~30% increase in exposure in moderate/severe impairment; no effect of mild/moderate renal impairment	Hepatic metabolism
Excretion routes	Feces (74.0% of dose) and urine (17.5% of dose)	Feces (69.1% of dose) and urine (22.6% of dose)	Biliary excretion
DDI	CYP3A inhibitors, CYP3A inducers, CYP3A substrates	CYP3A4 inhibitors, CYP3A4 inducers, CYP3A4 substrates	CYP3A inhibitors, CYP3A inducers
Food interaction	**Food intake reduces intersubject variability in exposure**	**Food intake does not affect overall exposure**	**Food intake does not affect overall exposure**

½ life, half-life; ADME, absorption, distribution, metabolism, excretion; DDI, drug-drug interaction; NA, not available; T_{max}, time to reach mean maximum concentration (C_{max}).

1. Ibrance [prescribing information]. Pfizer; 2016; 2. Infante JR, et al. ASCO 2014, abstract 2528 [poster]; 3. Juric D, et al. SABCS 2014, abstract P5-19-24 [poster]; 4. O'Sullivan CC, et al. *Int J Cancer Clin Res*. 2015;2:4; 5. Novartis data on file; 6. Dhuria SV, et al. ASCO 2015, abstract e13577; 7. Tolaney SM, et al. ASCO 2015, abstract 522; 8. Llombart A, et al. SABCS 2014, abstract OT1-1-07l 9. Patnaik A, et al. *Cancer Discov*. 2016;6(7):740-753; 10. Turner K, et al. AACR 2016. abstract CT152 [poster]; 11. Kulanthaivel P, et al. AACR 2016. abstract CT153 [poster]; 12. Shapiro GI, et al. ASCO 2013, abstract 2500 [oral].

Class Effects With CDK4/6 Inhibitors*

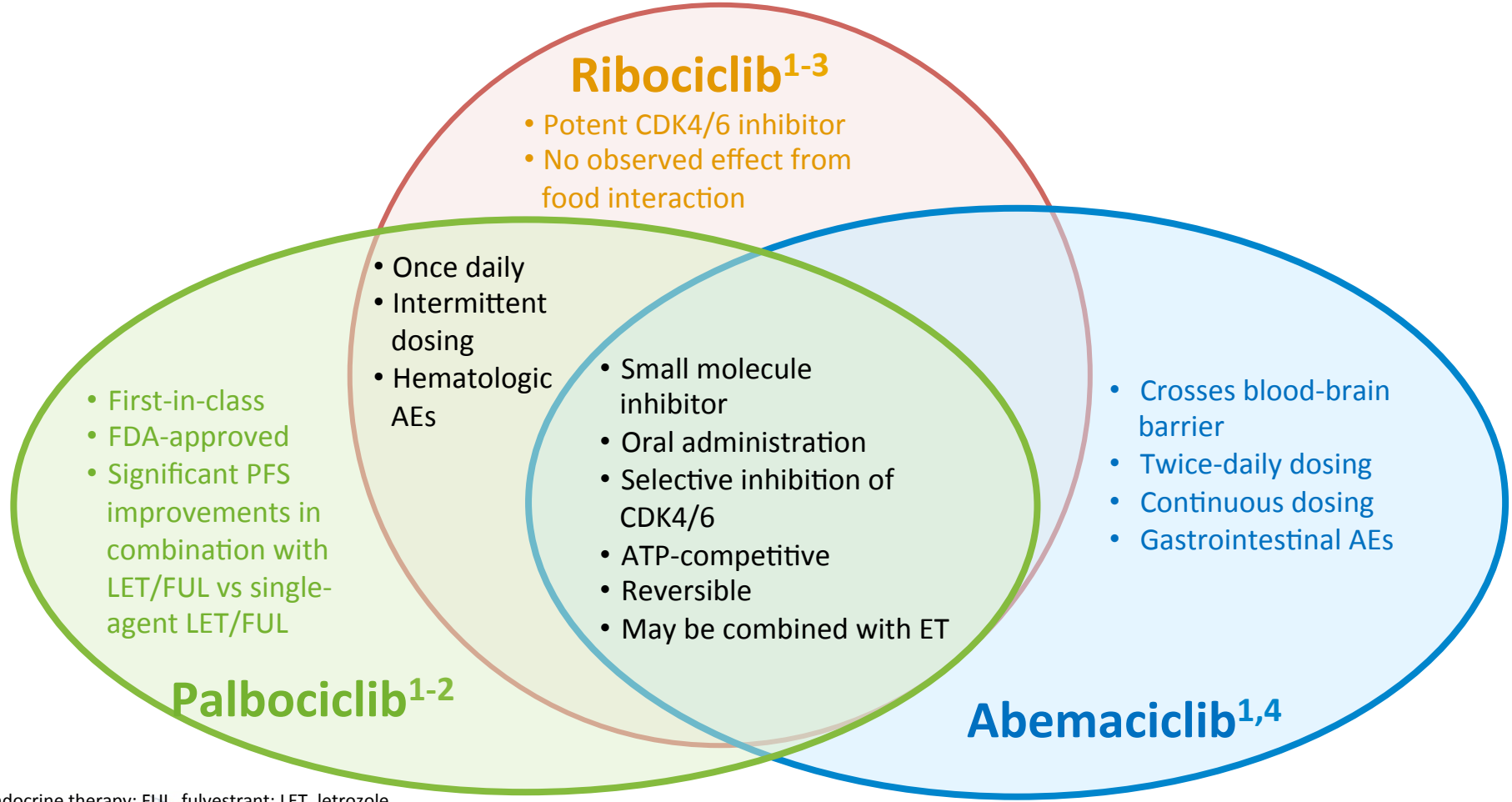
	Abemaciclib Single Agent[1]		Ribociclib Single Agent[2]		Palbociclib + Letrozole[3]		Ribociclib + Letrozole[4]		Abemaciclib + Fulvestrant[5]		Palbociclib + Fulvestrant[6]	
	N = 132		N = 63		N =444		N = 47		N = 19		N = 345	
AEs, %	**All Gr**	**Gr 3/4**	**All Gr**	**Gr 3 /4**	**All Gr**	**Gr 3 /4**	**All Gr**	**Gr 3 /4**	**All Gr**	**Gr 3/4**	**All Gr**	**Gr 3 /4**
Neutropenia	87.7	26.9	46	29	80	66	70	43	42.1	31.6	78.8	62.0
Anemia	68.5	0	30	3	24	5	23	0	15.8	10.5	26.1	2.6
Thrombocyto-penia	41.4	2.3	37	10	16	1	NA	NA	15.8	0	19.4	2.3
Leukopenia	90.8	27.7	48	21	24	1	NA	NA	36.8	26.3	45.5	25.2
Diarrhea	90.2	19.7	22	3	26	1	23	0	78.9	5.3	19.1	0
Nausea	64.2	4.5	46	2	35	<1	43	0	63.2	0	29.0	0
Vomiting	34.8	1.5	25	0	16	<1	15	0	42.1	5.3	14.5	0.3
ECG QT prolongation	NA	NA	8	0	NA	NA	NA	NA	NA	NA	NA	NA

^Note: Data shown are from multiple studies of CDK inhibitors as monotherapies or in combination with various endocrine therapy partners. Doses and terms for adverse events may vary between trials. Not intended for cross-comparison.

AE, adverse events; CDK, cyclin dependent kinase.

1. Dickler MN, et al. ASCO 2016. abstract 510 [oral]; 2. Infante. ASCO 2014, abstract 2528 [poster]; 3. Finn R, et al. ASCO 2016, abstract 507 [oral]; 4. Juric D, et al. ASCO 2016, abstract 568 [poster]; 5. Tolaney. SABCS 2014, abstract P5-19-13 [poster]; 6. Turner N, et al. *N Engl J Med*. 2015;373(3):209-219.

CDK4/6 Inhibitors: Summary of Similarities and Differences



ET, endocrine therapy; FUL, fulvestrant; LET, letrozole.

1. Sherr CJ, et al. *Cancer Discovery*. 2016;6(4):1-15; 2. O'Sullivan CC *Int J Cancer Clin Res*. 2015;2:029;
3. Dhuria SV, et al. ASCO 2015, abstract e13577; 4. Raub TJ, et al. *Drug Metab Dispos*. 2015;43(9)1630-1367.

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AGO-B BREAST STUDY GROUP

NSABP Foundation, Inc. Partners In Cancer Research

BIG Breast International Group

GBG GERMAN BREAST GROUP

PENELOPE^{B}

Phase III study evaluating palbociclib (PD-0332991), a Cyclin-Dependent Kinase (CDK) 4/6 Inhibitor in patients with hormone-receptor-positive, HER2-normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy

GBG-78 / BIG 01-13 / NSABP B-54-I

Status

30-September-2016

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PALLAS
PALbociclib CoLlaborative Adjuvant Study

CRA / CSM TRAINING
June 30th, 2016

Protocol Overview

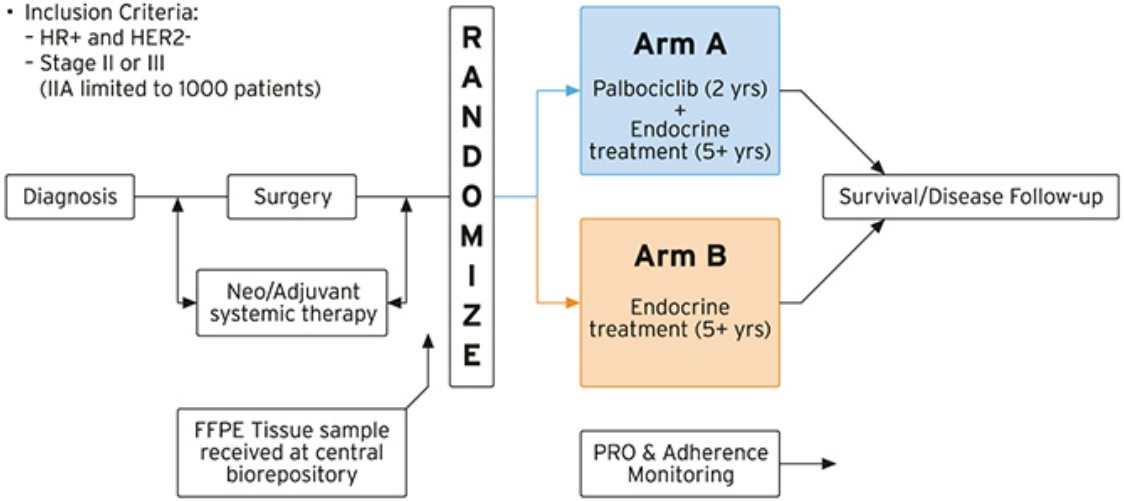
Anita Jallitsch-Halper
ABCSG Project Management

Sponsored by AFT and ABCSG, in cooperation with PrECOG, BIG, GBG, NSABP, and supported by Pfizer.

PALLAS SCHEMA

Patient Population:

- N = 4600
- Inclusion Criteria:
  - HR+ and HER2-
  - Stage II or III
    (IIA limited to 1000 patients)



Stratification Factors:

- Anatomic stage (IIA vs IIB/III), assessed by pathologic staging or by clinical staging if pre-operative therapy was given with the higher stage determining eligibility
- Neo/adjuvant chemotherapy (yes vs no),
- Age (≤ 50 vs > 50 years),
- Geographic region (North America vs Europe vs Other)

Arm A: palbociclib at a dose of 125 mg once daily, Day 1-21 in a 28-day cycle for total duration of 2 years, in addition to standard adjuvant endocrine therapy

Arm B: standard adjuvant endocrine therapy (AI, tamoxifen, LHRH agonist)