STANFORD
CANCER INSTITUTE

Endocrine Therapy in Breast Cancer: State of the Art

12 AUG 2018

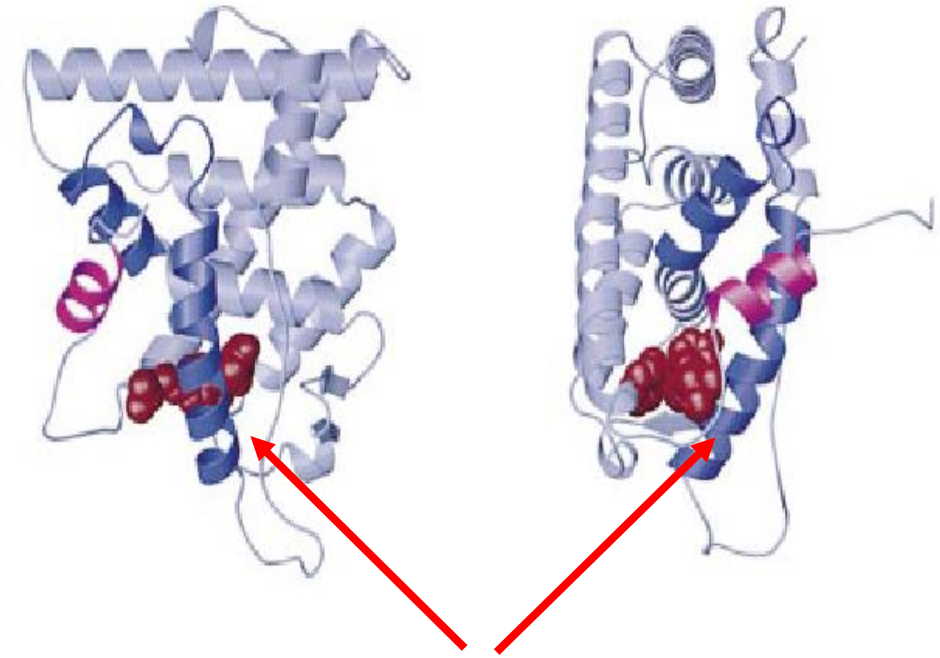
Mark Pegram, M.D.
Susy Yuan-Huey Hung Professor of Oncology
Associate Director for Clinical Research
Director, Stanford Breast Oncology Program
Associate Dean for Clinical Research Quality
Stanford University School of Medicine

Oophorectomy and Clinical Response in Breast Cancer

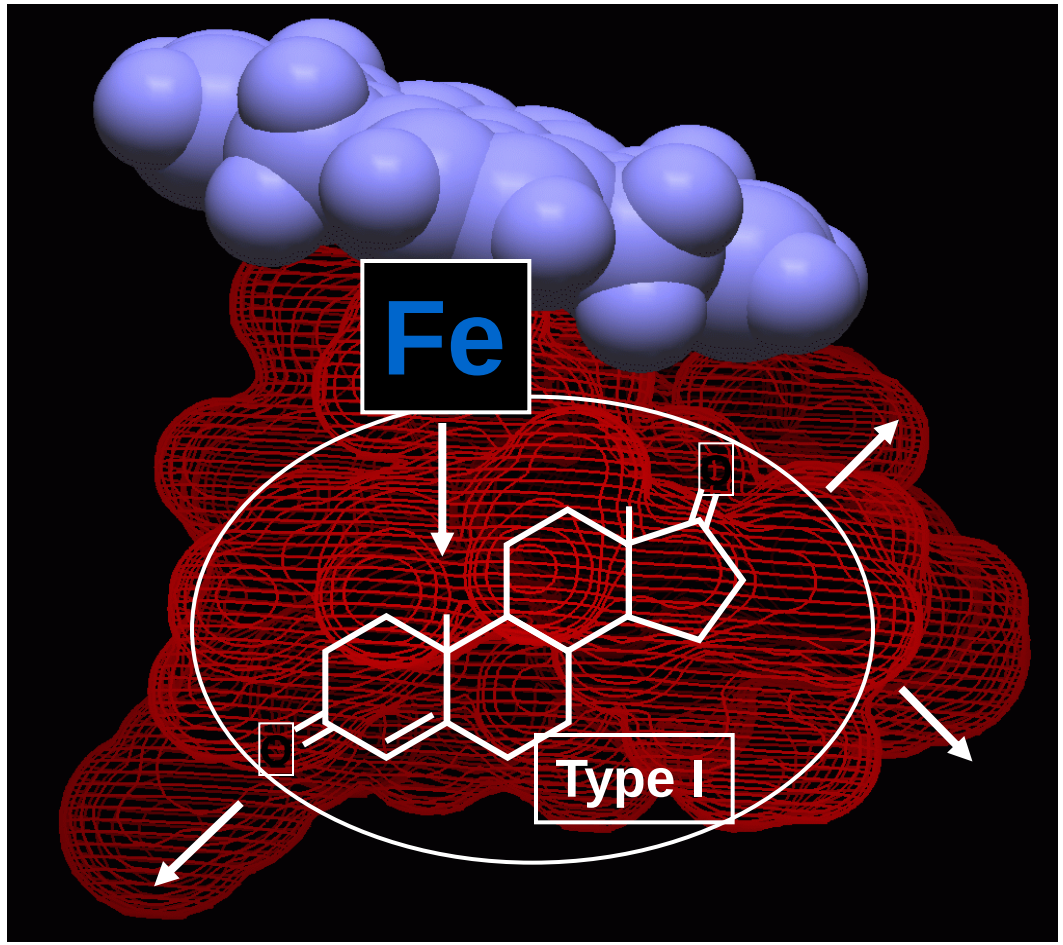
Sir George Beatson, The Lancet, 1896

LEFT: SERM binding to ER alters conformation of helix 12 and disrupts interaction with ER co-activators
RIGHT: Type I (steroidal) Aromatase Inhibitor

ERα/Tamoxifen

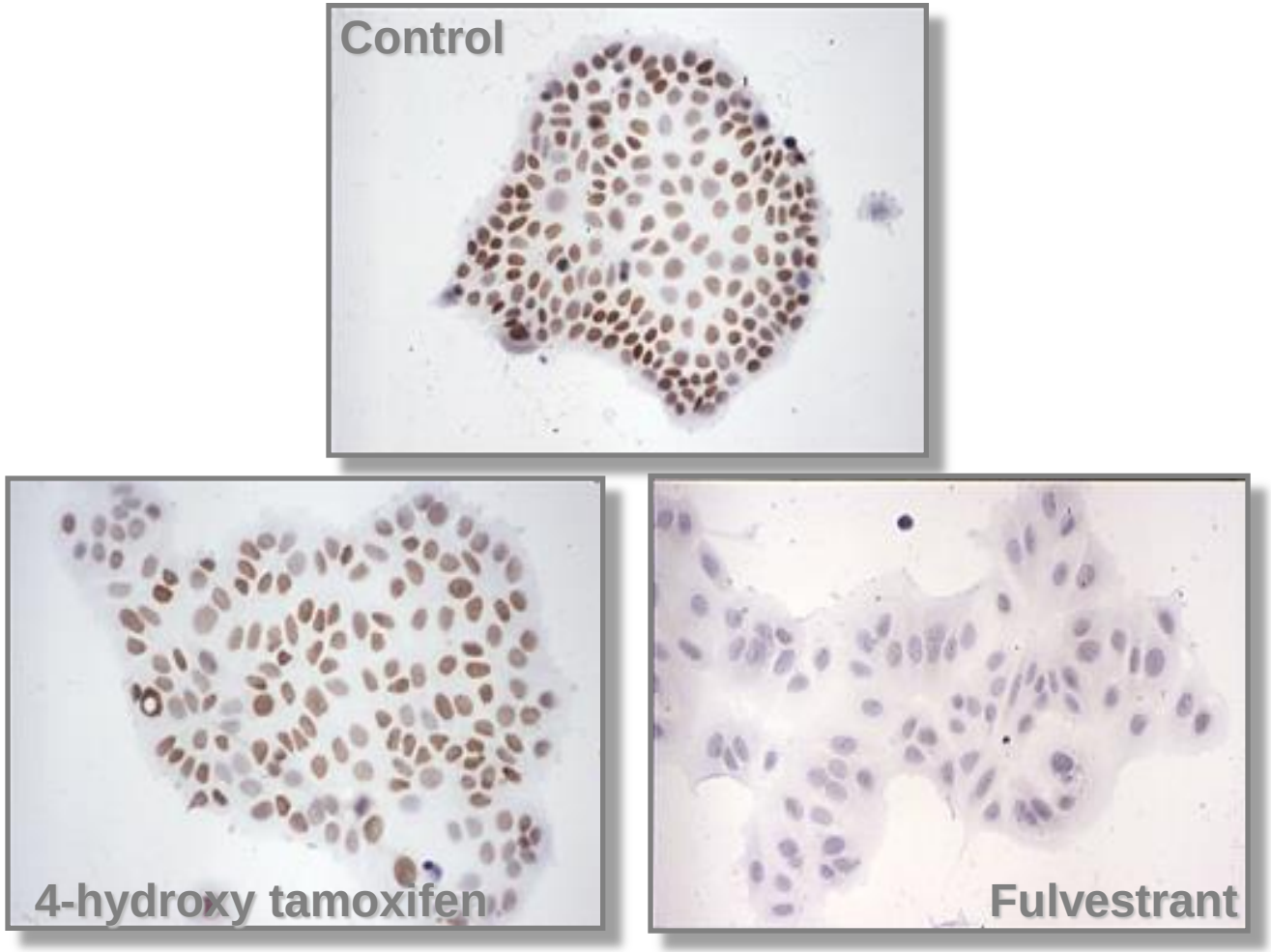


Helix 12

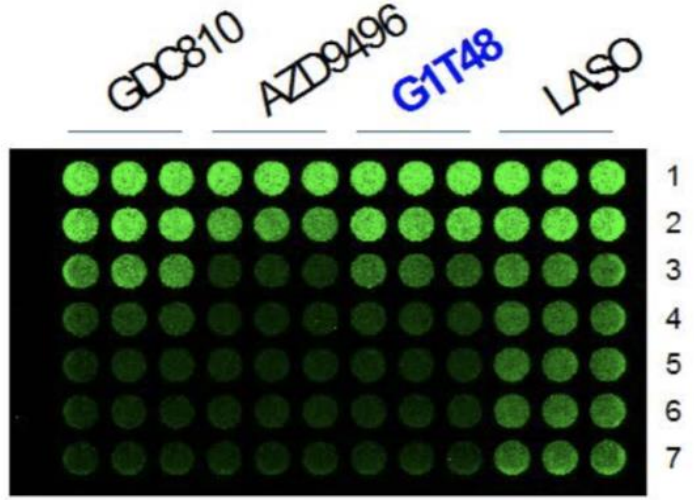


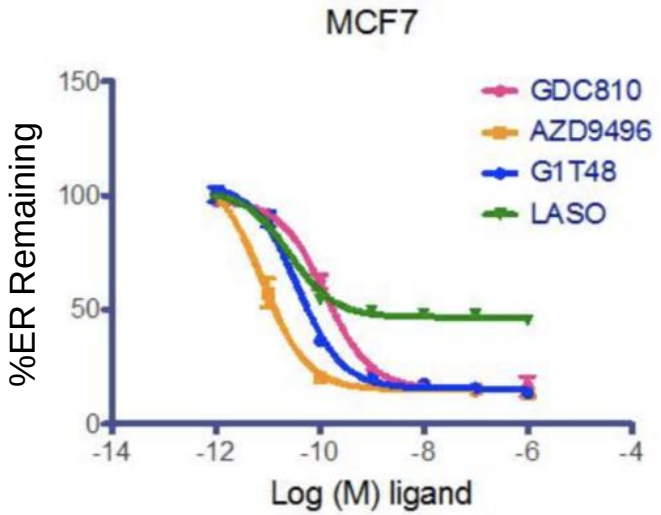
*Computer-assisted molecular modeling.
Furet et al. *J Med Chem*. 1993;36:1393.

Downregulation of ER by Fulvestrant and G1T48 in Human Breast Cancer Cell Lines



Reproduced courtesy of Professor R Nicholson, Tenovus Institute for Cancer Research, Cardiff, UK. *Fulvestrant is ICI 182,780*
See Nicholson R et al. *Ann New York Acad Sci*. 1995;761:148-163.

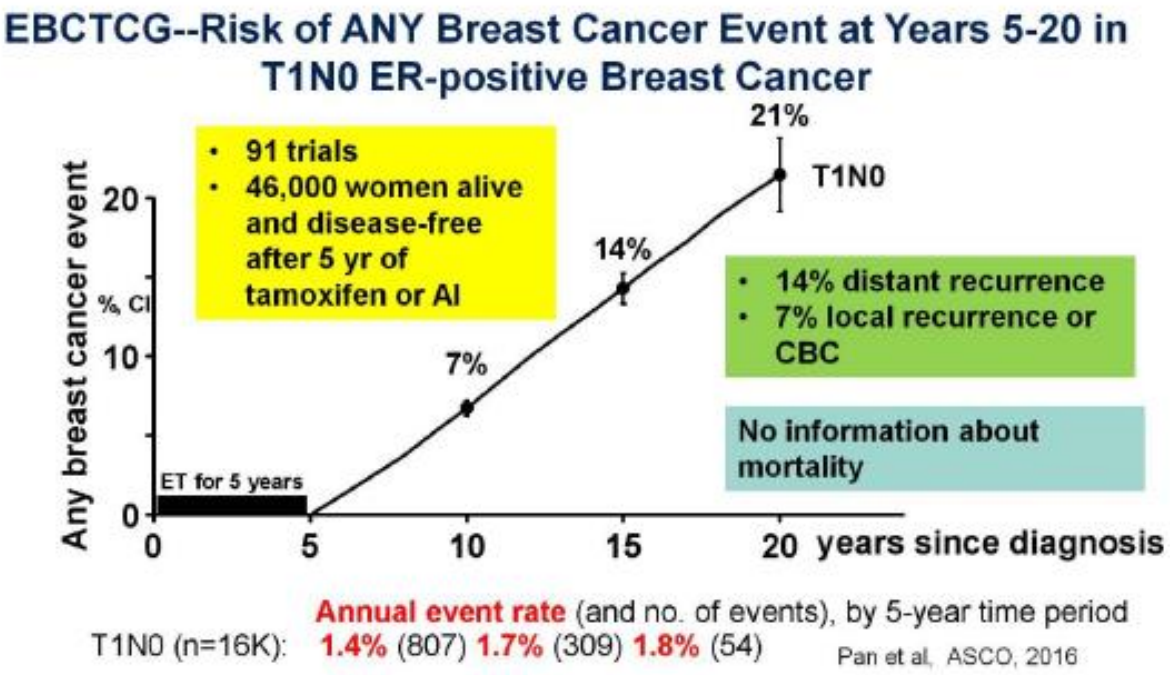




ER protein expression (top panels, green) was assessed using In-cell Western

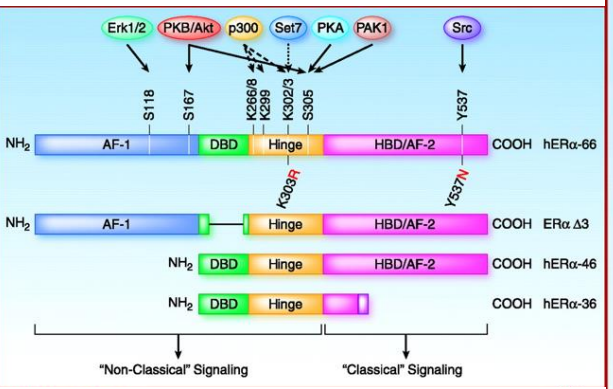
Recurrence/Resistance After Endocrine Therapy for Breast Cancer Represents a Substantial Unmet Need

- Early Breast Cancer Trialists' Collaborative Group (EBCTCG)
- N=46,000 women enrolled in 91 trials who were disease-free after initial 5 years of endocrine therapy
  - Observed a risk of distant recurrence of 7% to 21% from year 10 to year 20
  - Degree of risk was dependent on stage, tumor grade, and expression of Ki67

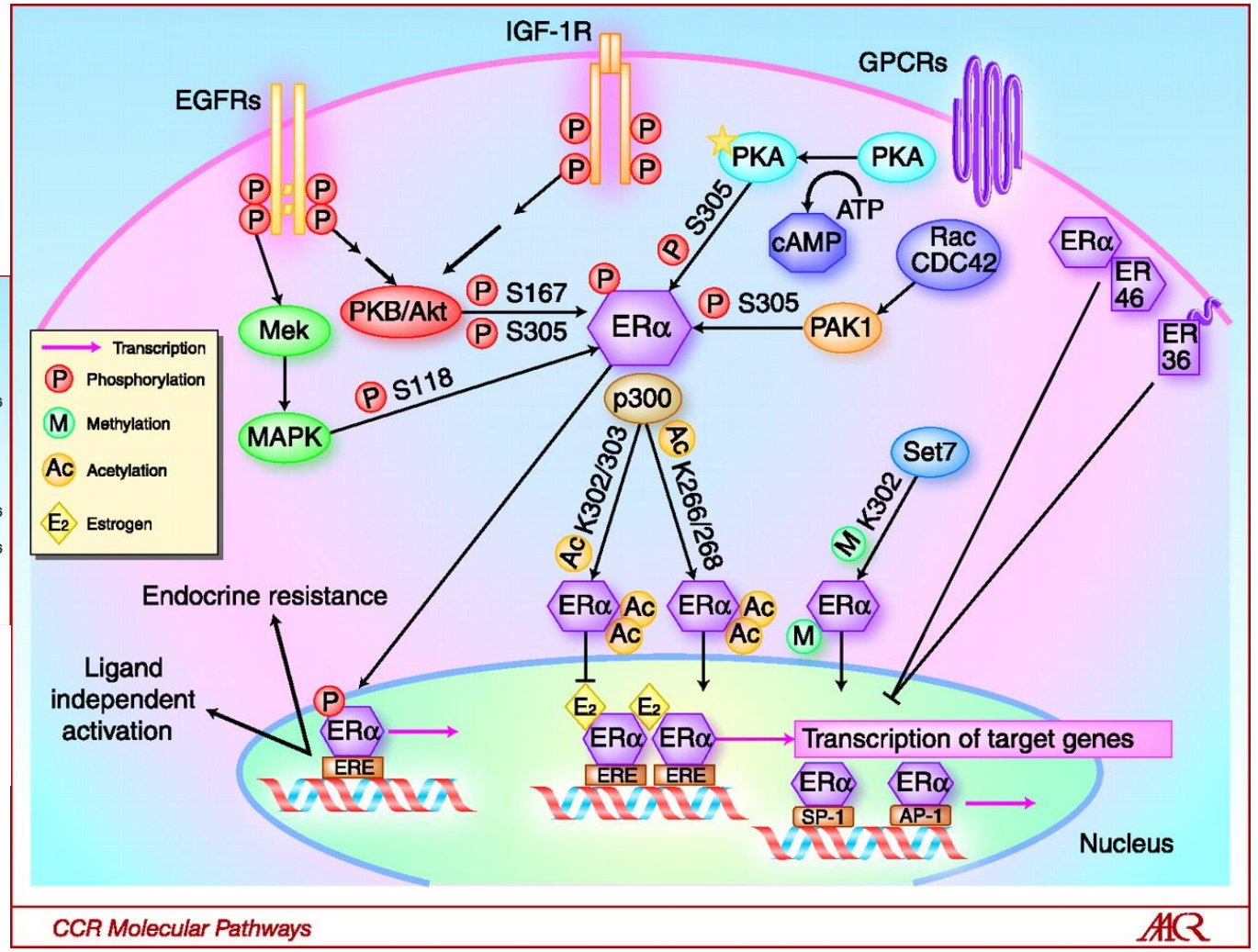


Pan et al, ASCO 2016

A representation of the “classical” and “nonclassical” estrogen receptor signaling pathways.



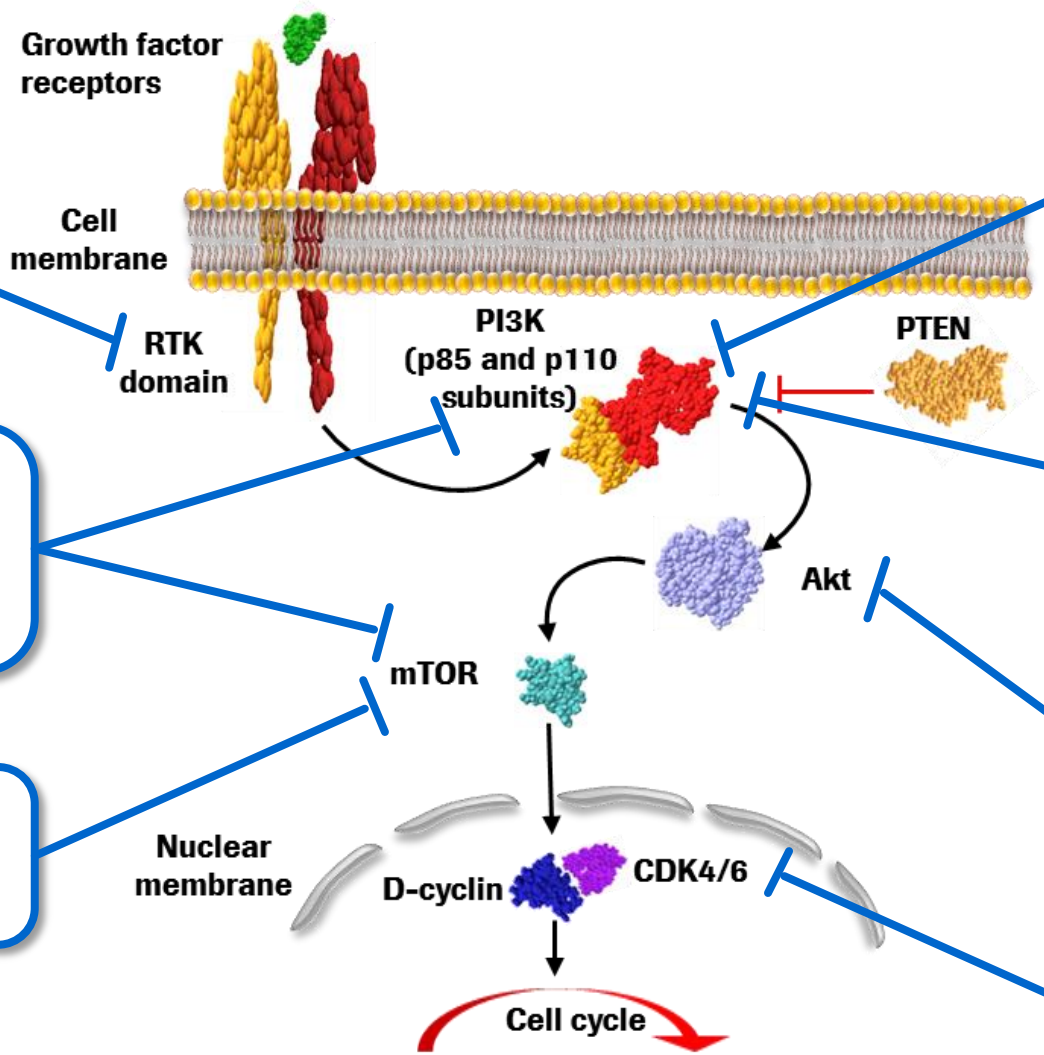
Sites of post-translational modifications, and mutations within ERα



Ines Barone et al. Clin Cancer Res 2010;16:2702-2708

Clinical Cancer Research
AACR American Association for Cancer Research

The PI3K-AKT-mTOR Pathway is Under Investigation as a Potential Target to Overcome Endocrine Resistance in HR+ mBC



Lapatinib
Trastuzumab
Pertuzumab

PI3K/mTOR inhibitors[1–3]
Apitolisib
LY3023414
Gedatolisib

mTOR inhibitor[1,2]
Everolimus
Vistusertib

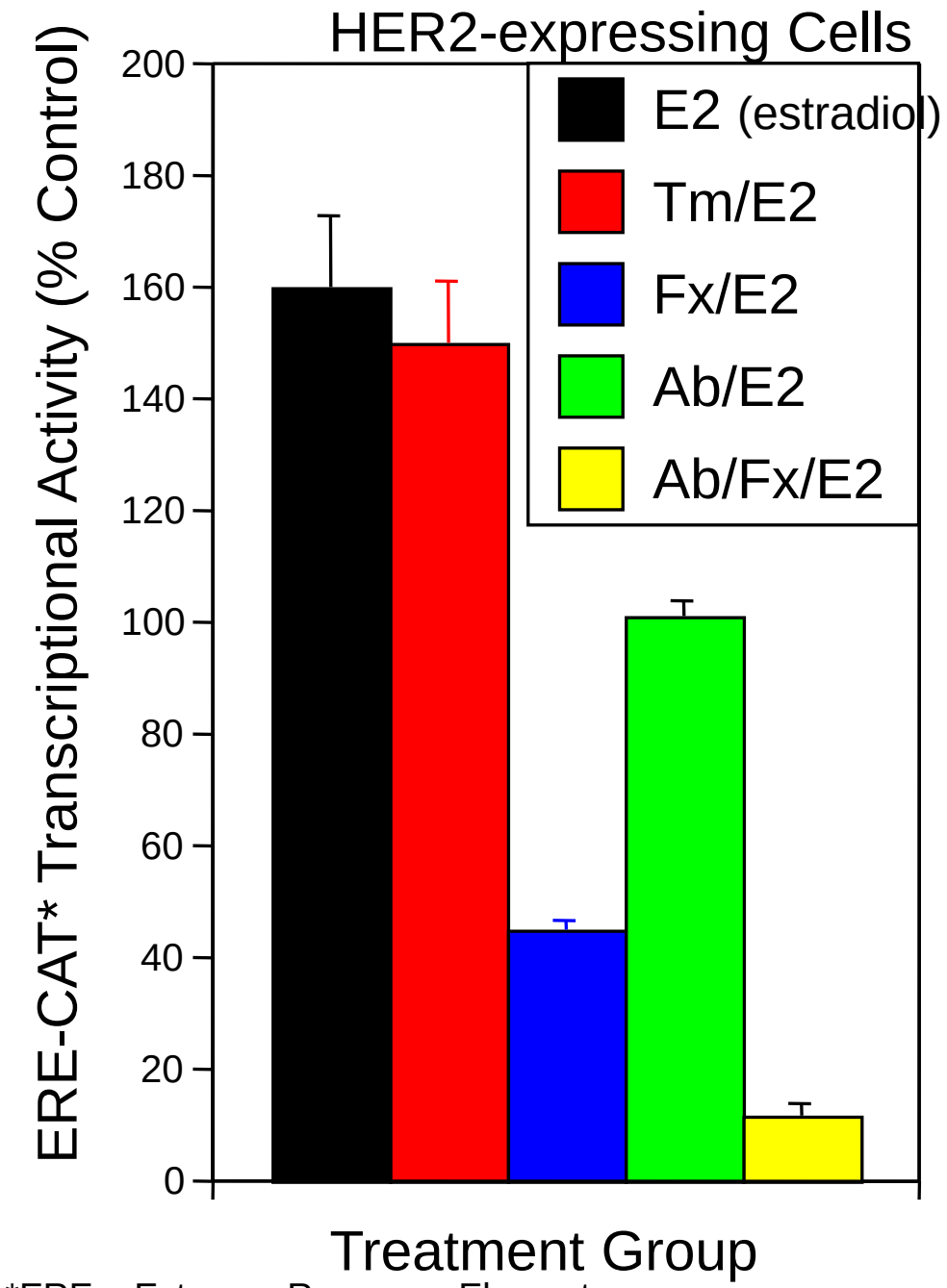
Pan-PI3K inhibitors[1]
Buparlisib
Pictilisib
Pilaralisib
PX-866

Selective PI3K inhibitors[1]
Alpelisib (α-specific)
Taselisib (β-sparing)
GDC-007 (α-specific)
MLN01117 (α-specific)
GSK2636771 (b-specific)
AZD8186 (b-specific)
IPI-549 (g-specific)

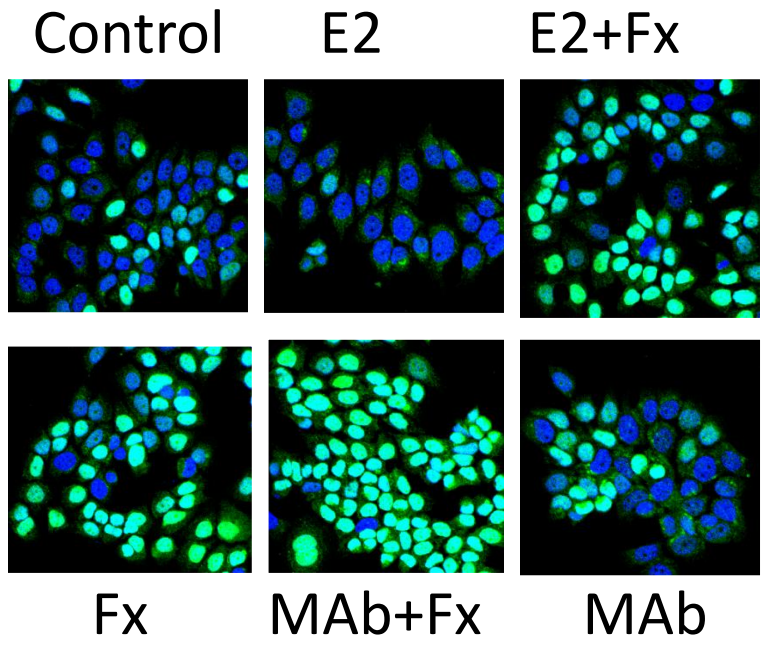
Akt inhibitors[1–3,5]
MK-2206
Ipatasertib
AZD5363

CDK4/6 inhibitors[1,3]
Palbociclib
Abemaciclib
Ribociclib

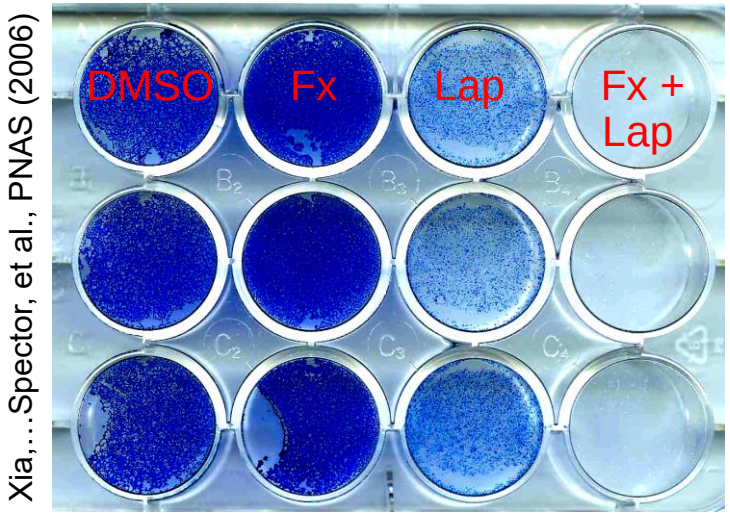
1. Janku F. Can Treat Rev. 2017; 2. Rodon J, et al. Nat Rev Clin Oncol 2013;
3. Ciruelos Gil EM. Cancer Treat Rev 2014; 4. National Cancer Institute;
5. Addie M, et al. J Med Chem 2013; 6. Martini M, et al. Front Oncol 2013.



*ERE = Estrogen Response Element
CAT = Chloramphenicol Acetyl Transferase
Fx = Fulvestrant

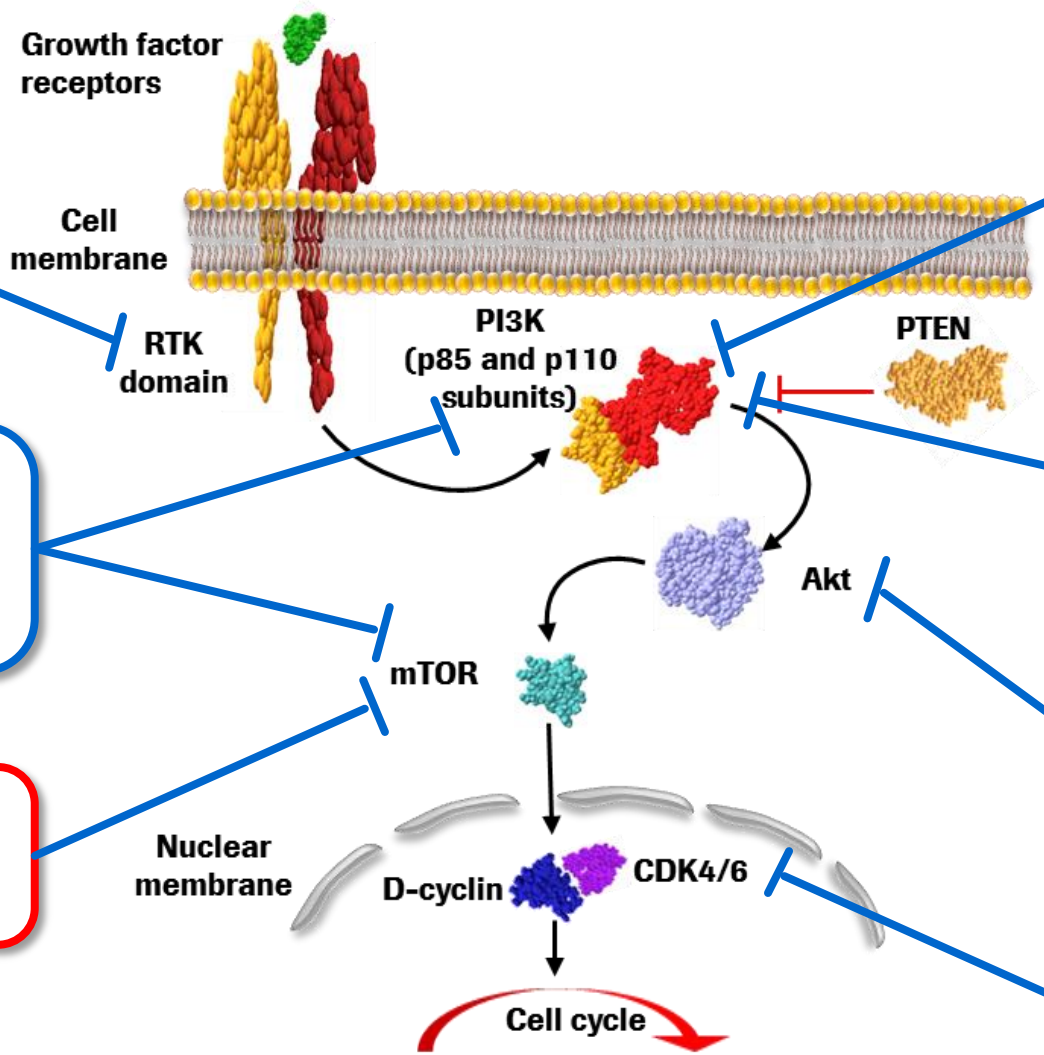


p27 = cdk inhibitor = cell cycle arrest = green



Pietras RJ, Arboleda J, Reese DM, Wongvipat N, Pegram MD, Ramos L, Gorman CM, Parker MG, Sliwkowski MX, Slamon DJ Oncogene. 1995 Jun 15;10(12):2435-46.

The PI3K-AKT-mTOR Pathway is Under Investigation as a Potential Target to Overcome Endocrine Resistance in HR+ mBC



Lapatinib
Trastuzumab
Pertuzumab

PI3K/mTOR inhibitors[1–3]
Apitolisib
LY3023414
Gedatolisib

mTOR inhibitor[1,2]
Everolimus
Vistusertib

Pan-PI3K inhibitors[1]
Buparlisib
Pictilisib
Pilaralisib
PX-866

Selective PI3K inhibitors[1]
Alpelisib (α-specific)
Taselisib (β-sparing)
GDC-007 (α-specific)
MLN01117 (α-specific)
GSK2636771 (b-specific)
AZD8186 (b-specific)
IPI-549 (g-specific)

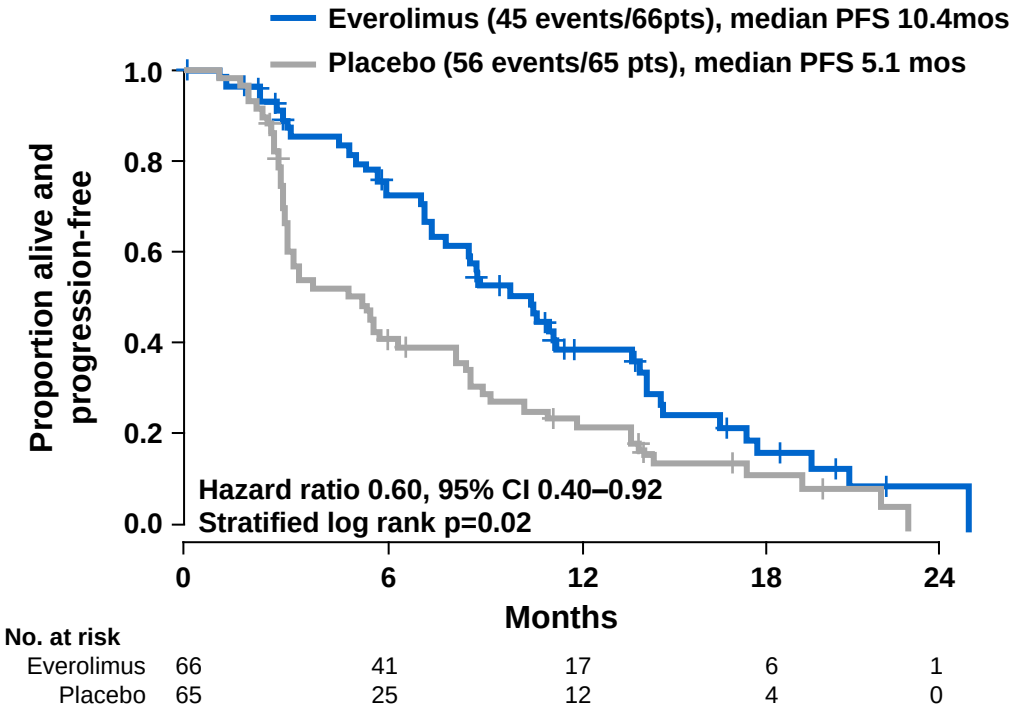
Akt inhibitors[1–3,5]
MK-2206
Ipatasertib
AZD5363

CDK4/6 inhibitors[1,3]
Palbociclib
Abemaciclib
Ribociclib

1. Janku F. Can Treat Rev. 2017; 2. Rodon J, et al. Nat Rev Clin Oncol 2013;
3. Ciruelos Gil EM. Cancer Treat Rev 2014; 4. National Cancer Institute;
5. Addie M, et al. J Med Chem 2013; 6. Martini M, et al. Front Oncol 2013.

PrECOG 0102: fulvestrant ± everolimus -- efficacy and safety

Primary endpoint: PFS by investigator assessment



OS

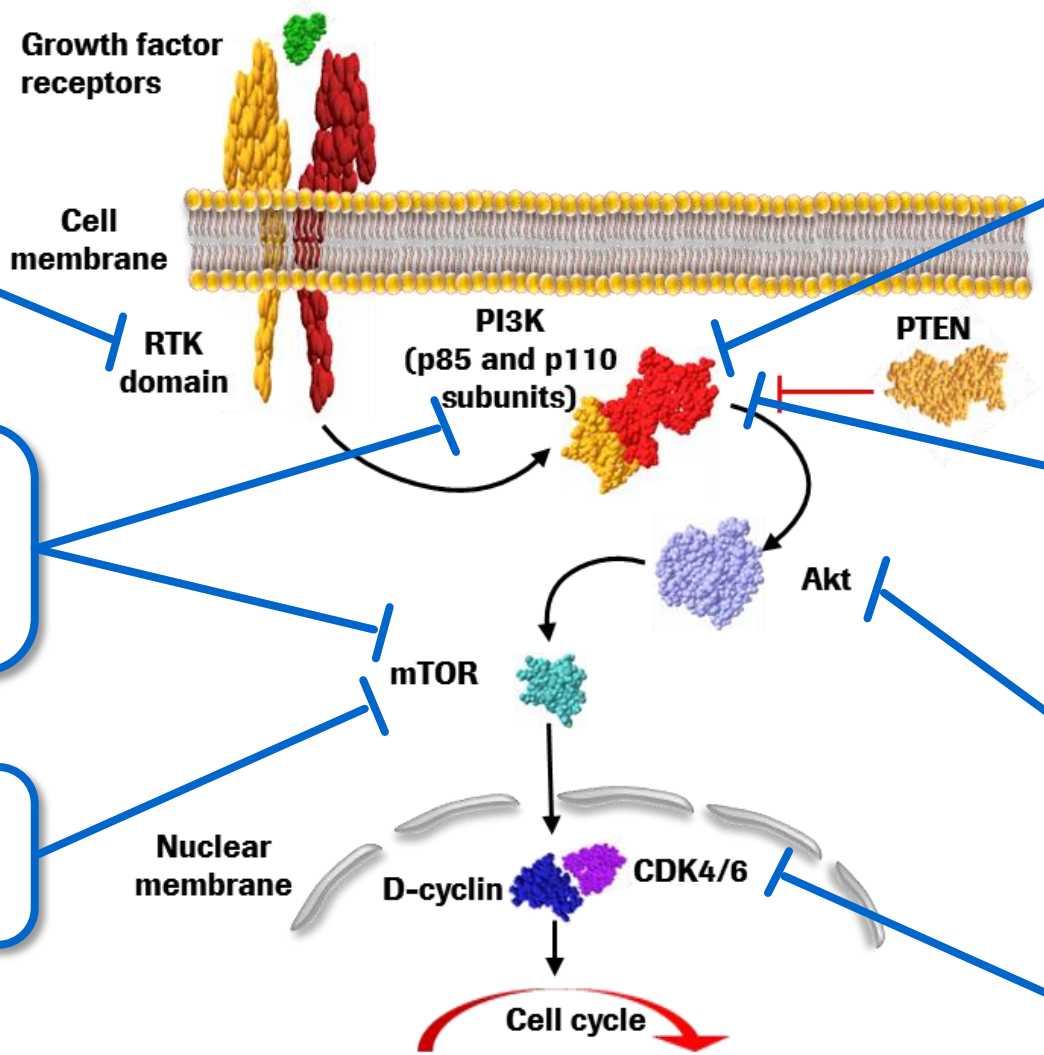
- Median OS: 24.8 months with fulvestrant + everolimus vs. not reached with fulvestrant + placebo

Safety

- The most frequently reported AEs with fulvestrant + everolimus were mucositis/stomatitis, fatigue, anaemia and hypertriglyceridaemia

Kornblum NS, et al. *Cancer Res.* 2017;77(4_Suppl):Abstract S1

The PI3K-AKT-mTOR Pathway is Under Investigation as a Potential Target to Overcome Endocrine Resistance in HR+ mBC



Lapatinib
Trastuzumab
Pertuzumab

PI3K/mTOR inhibitors[1–3]
Apitolisib
LY3023414
Gedatolisib

mTOR inhibitor[1,2]
Everolimus
Vistusertib

Pan-PI3K inhibitors[1]
Buparlisib
Pictilisib
Pilaralisib
PX-866

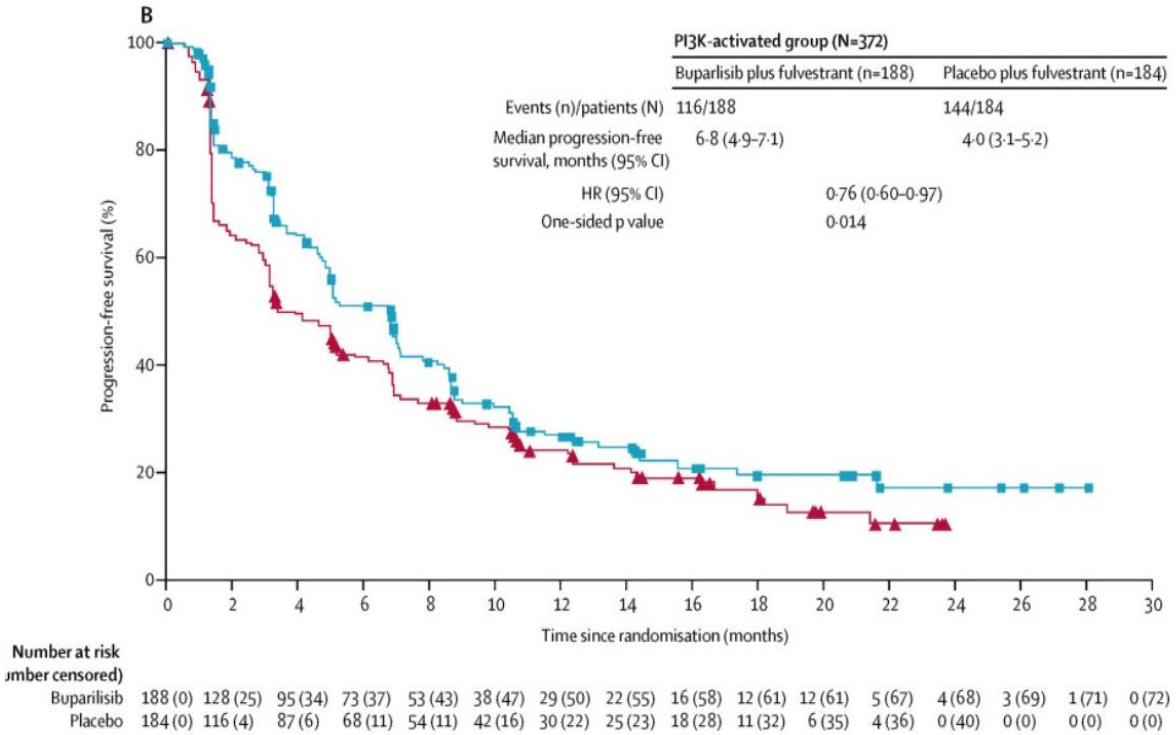
Selective PI3K inhibitors[1]
Alpelisib (α-specific)
Taselisib (β-sparing)
GDC-007 (α-specific)
MLN01117 (α-specific)
GSK2636771 (b-specific)
AZD8186 (b-specific)
IPI-549 (g-specific)

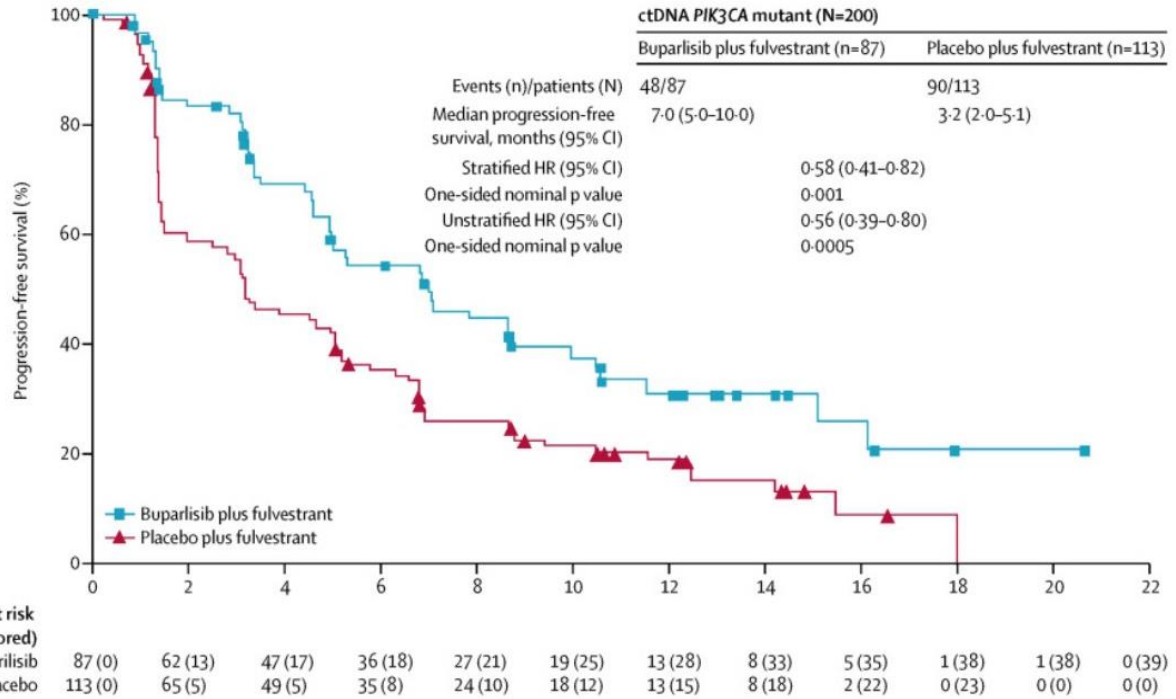
Akt inhibitors[1–3,5]
MK-2206
Ipatasertib
AZD5363

CDK4/6 inhibitors[1,3]
Palbociclib
Abemaciclib
Ribociclib

1. Janku F. Can Treat Rev. 2017; 2. Rodon J, et al. Nat Rev Clin Oncol 2013;
3. Ciruelos Gil EM. Cancer Treat Rev 2014; 4. National Cancer Institute;
5. Addie M, et al. J Med Chem 2013; 6. Martini M, et al. Front Oncol 2013.

BELLE-2
ctDNA Analysis of PI3K Status May be More Predictive than Archival Tissue
Overall concordance of PIK3CA status in tumour tissue and ctDNA was 342 (77%) of 446*





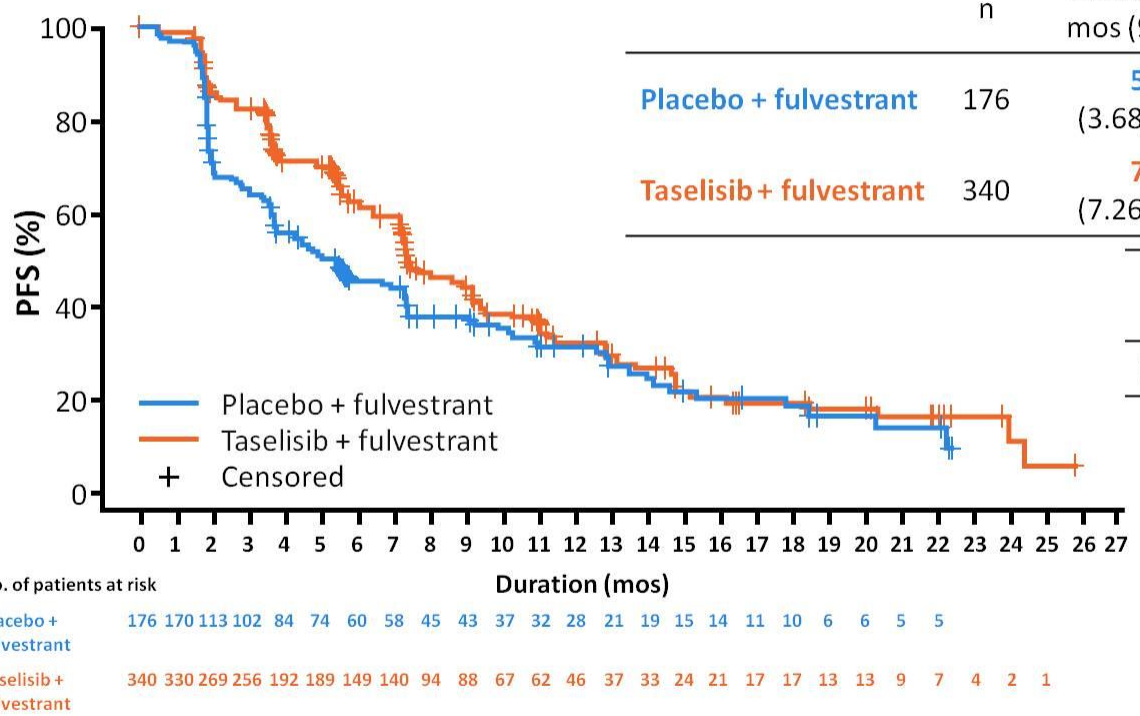
***In 307 patients with PIK3CA wild-type tumour tissue, 243 (79%) had non-mutant ctDNA, and 64 (21%) had PIK3CA mutant ctDNA, potentially indicating tumour evolution between initial diagnosis and treatment.**

Baselga J, et al. Lancet Oncol. 2017

SANDPIPER: Phase III study of taselisib + fulvestrant vs. fulvestrant alone in ER+ PIK3CA-mut MBC

PRIMARY ENDPOINT:

INV-PFS in patients with PIK3CA*-mutant tumors*



	n	Median PFS, mos (95% CI)	Stratified HR (95% CI)	p-value (stratified log rank)
Placebo + fulvestrant	176	5.4 (3.68, 7.29)		
Taselisib + fulvestrant	340	7.4 (7.26, 9.07)	0.70 (0.56, 0.89)	0.0037

	Placebo + fulvestrant	Taselisib + fulvestrant
Events	67.6%	57.1%

No. of patients at risk

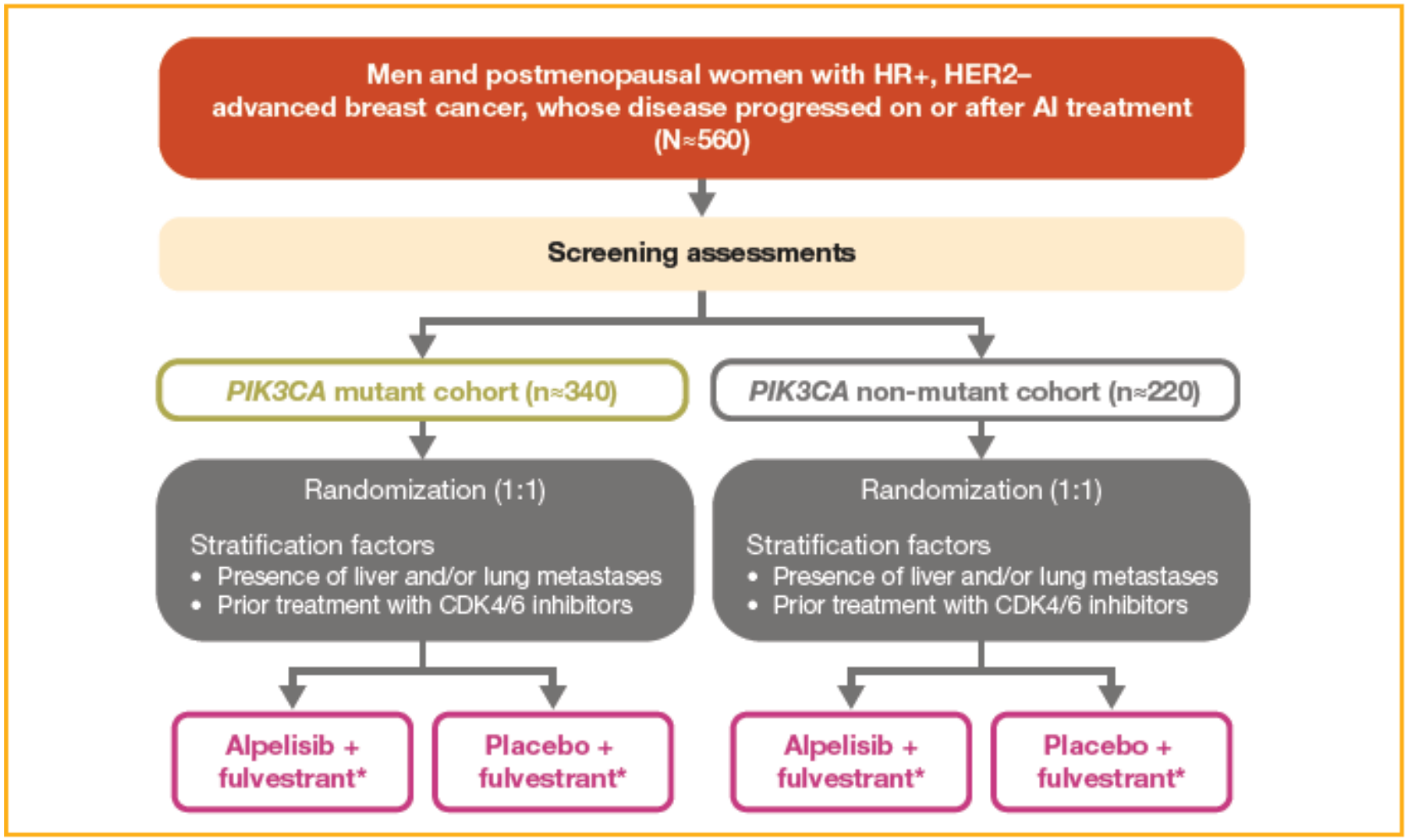
Placebo + fulvestrant	176	170	113	102	84	74	60	58	45	43	37	32	28	21	19	15	14	11	10	6	6	5	5		
Taselisib + fulvestrant	340	330	269	256	192	189	149	140	94	88	67	62	46	37	33	24	21	17	17	13	13	9	7	4	2	1

PFS was defined as the time from randomization to first disease progression as determined by investigator using RECIST v1.1, or death from any cause.
RECIST, Response Evaluation Criteria In Solid Tumors.

Grade ≥3 AEs = 49.5%; SAEs = 32%

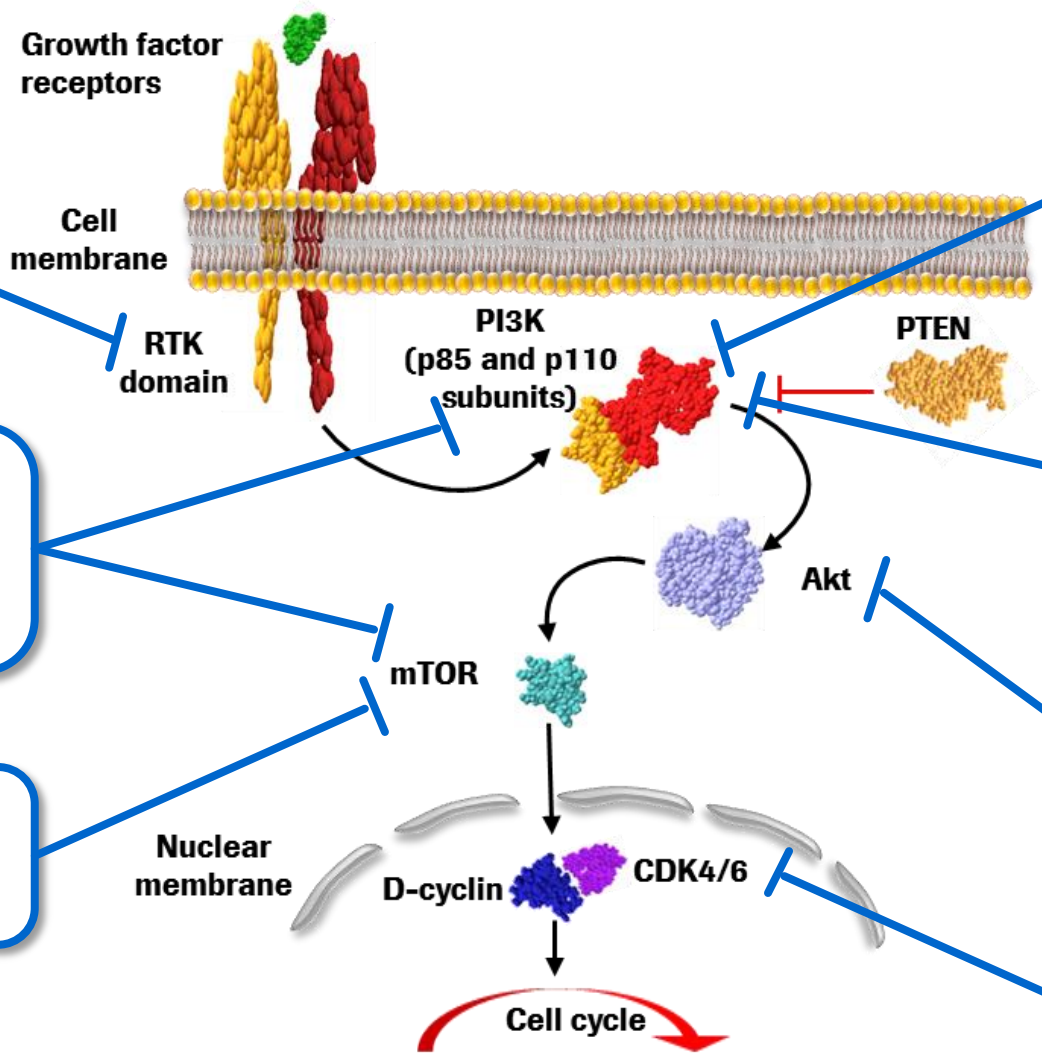
Presented By Jose Baselga at 2018 ASCO Annual Meeting

Phase III SOLAR 1 α-specific Alpelisib* + fulvestrant vs. fulvestrant + placebo in HR+HER2- AI resistant mBC



* Alpelisib (BYL719, Novartis) is the first oral PI3Ki to selectively target the class I PI3K a-isoform (IC50 = 4.6 nM).

The PI3K-AKT-mTOR Pathway is Under Investigation as a Potential Target to Overcome Endocrine Resistance in HR+ mBC



Lapatinib
Trastuzumab
Pertuzumab

PI3K/mTOR inhibitors[1–3]
Apitolisib
LY3023414
Gedatolisib

mTOR inhibitor[1,2]
Everolimus
Vistusertib

Pan-PI3K inhibitors[1]
Buparlisib
Pictilisib
Pilaralisib
PX-866

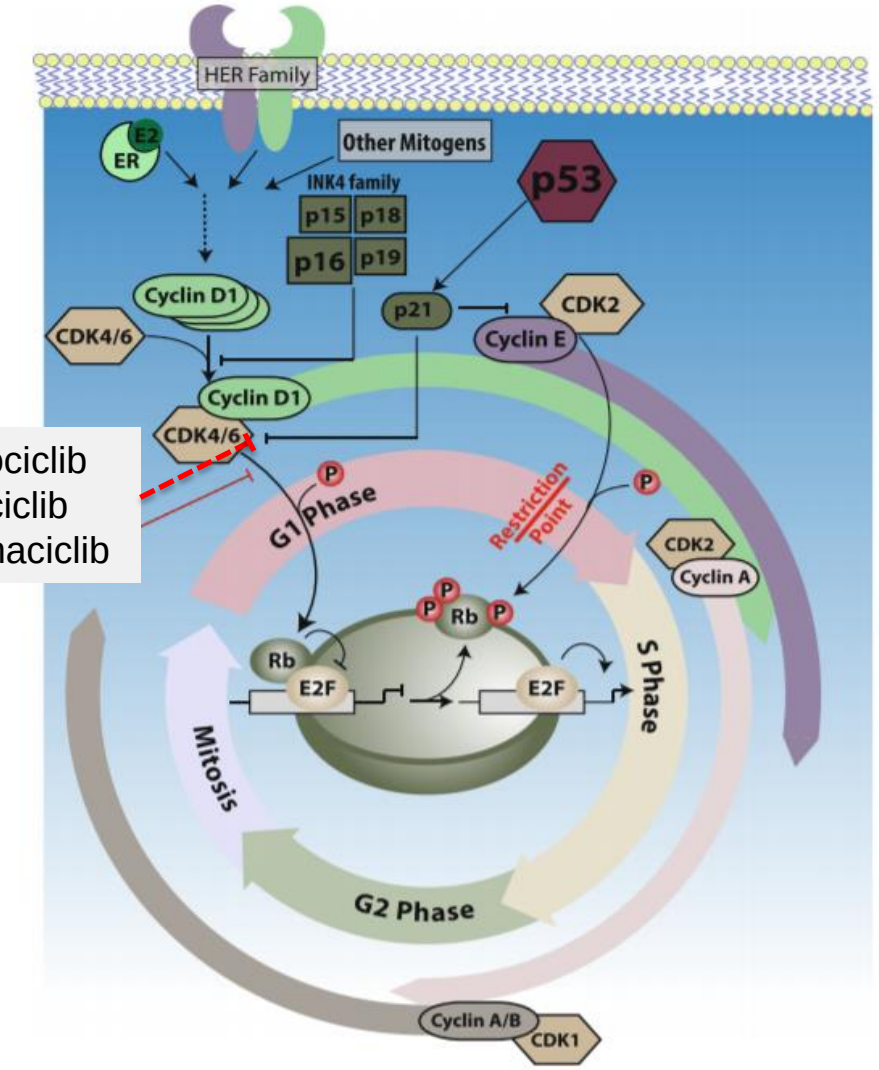
Selective PI3K inhibitors[1]
Alpelisib (α-specific)
Taselisib (β-sparing)
GDC-007 (α-specific)
MLN01117 (α-specific)
GSK2636771 (b-specific)
AZD8186 (b-specific)
IPI-549 (g-specific)

Akt inhibitors[1–3,5]
MK-2206
Ipatasertib
AZD5363

CDK4/6 inhibitors[1,3]
Palbociclib
Abemaciclib
Ribociclib

1. Janku F. Can Treat Rev. 2017; 2. Rodon J, et al. Nat Rev Clin Oncol 2013;
3. Ciruelos Gil EM. Cancer Treat Rev 2014; 4. National Cancer Institute;
5. Addie M, et al. J Med Chem 2013; 6. Martini M, et al. Front Oncol 2013.

The Role of CDK4/6 in HR-Positive Breast Cancer



Finn RS, et al. Breast Cancer Res. 2016;18(1):17.

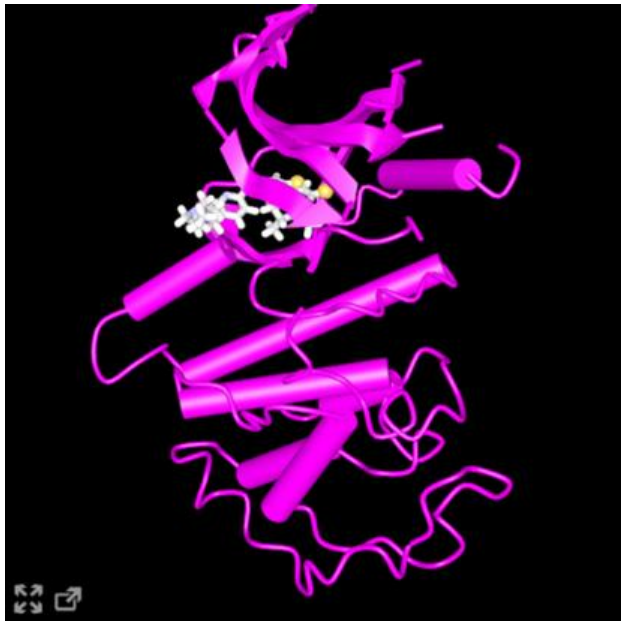
- 2001 Nobel Prize in physiology and medicine for Hartwell (cdc, yeast), Nurse (CDK, human) and Hunt (cyclins, sea urchin)
- The growth of HR+ breast cancer is dependent on Cyclin D1, a direct transcriptional target of ER
- Cyclin D1 activates CDK 4/6 resulting in G1–S phase transition and entry into the cell cycle
- Rb binding inactivates E2F, which regulates genes important for transition through the G1/S cell cycle restriction point[1,2]
- Phosphorylation of Rb by CDK4/6 leads to dissociation of E2F from Rb and cell cycle progression[1,2]

CDK, cyclin-dependent kinase; Rb, retinoblastoma

1. Hosford S, et al. Pharmgenomics Pers Med. 2014;7:203-215.
2. Thangavel C, et al. Endocr Relat Cancer. 2011;18(3):333-345.

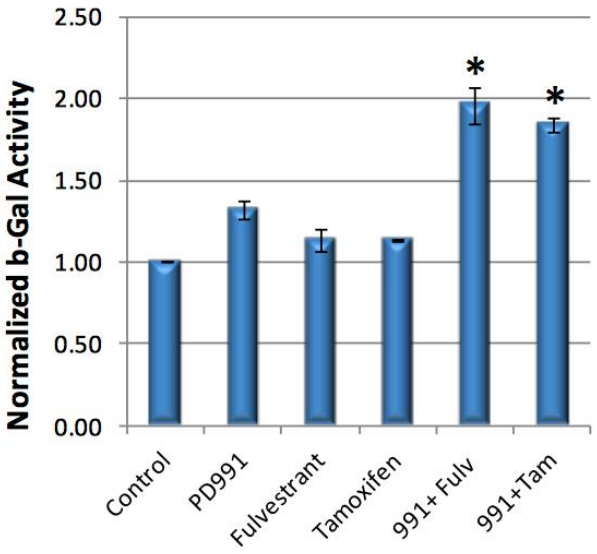
Molecular Mechanisms of CDK4/6 Inhibitors Combined With ER Antagonists in ER+ Breast Cancer

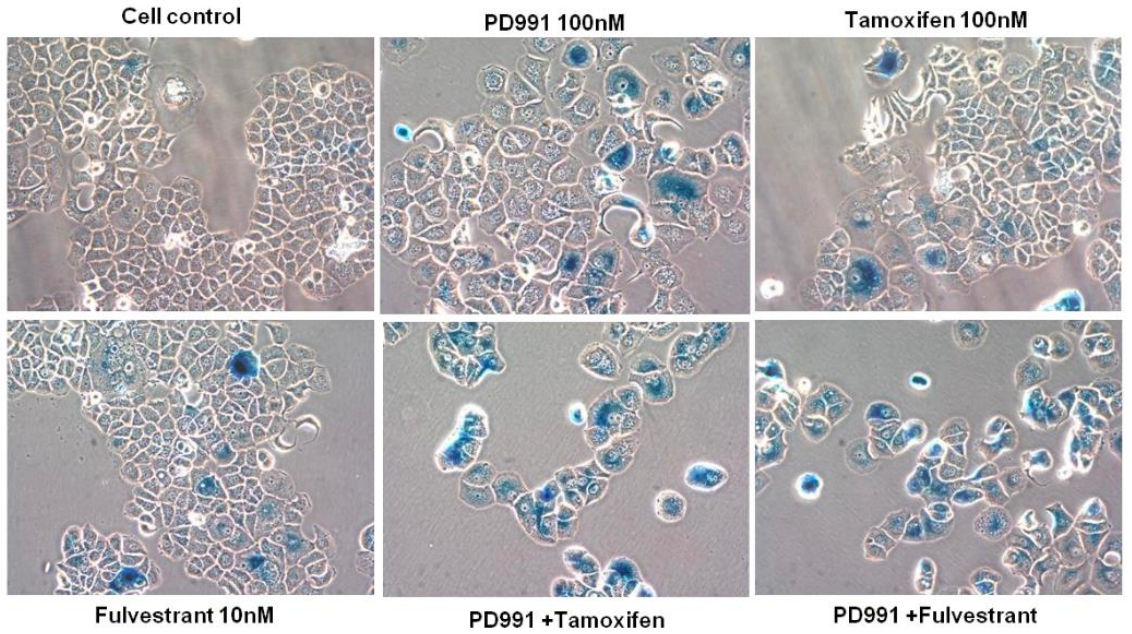
- Combined inhibition of CDK4/6 and ER signaling increases senescence in ER+ breast cancer cell lines



X-Ray Co-Crystal Structure of Human CDK6 and Abemaciclib

SA**-βGal activity in T47D treated with ER antagonists and palbociclib



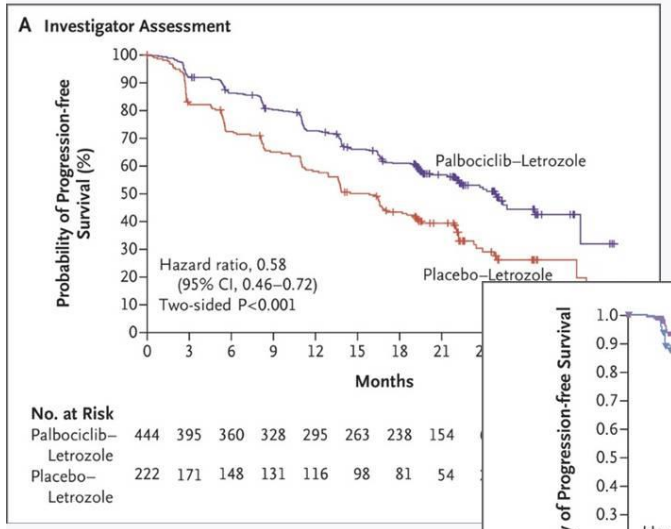


*P<.001 vs single agents
**SA, senescence-associated

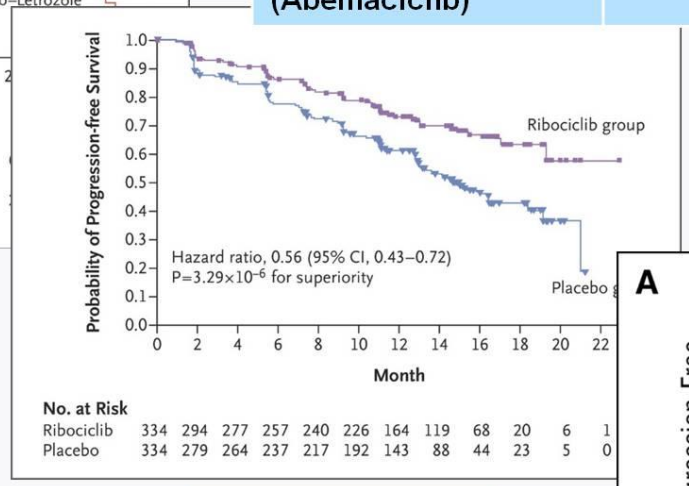
Finn RS, et al. Breast Cancer Res. 2009;11(5):R77.

First-line Metastatic ER+/HER2- Breast Cancer
PALOMA-2, MONALEESA 2, and MONARCH 3

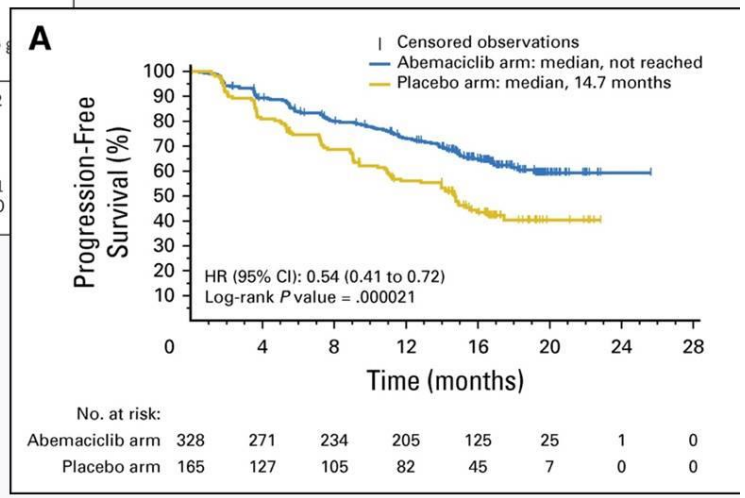
	HR	AI-Placebo	AI- CDK4/6i
PALOMA 2 (Palbociclib)	0.58	14.5 m	24.8 m
MONALEESA 2 (Ribociclib)	0.56	14.7 m	Not Reached
MONARCH 3 (Abemaciclib)	0.54	14.7 m	Not Reached



ORR: 55.3%



ORR: 52.7%



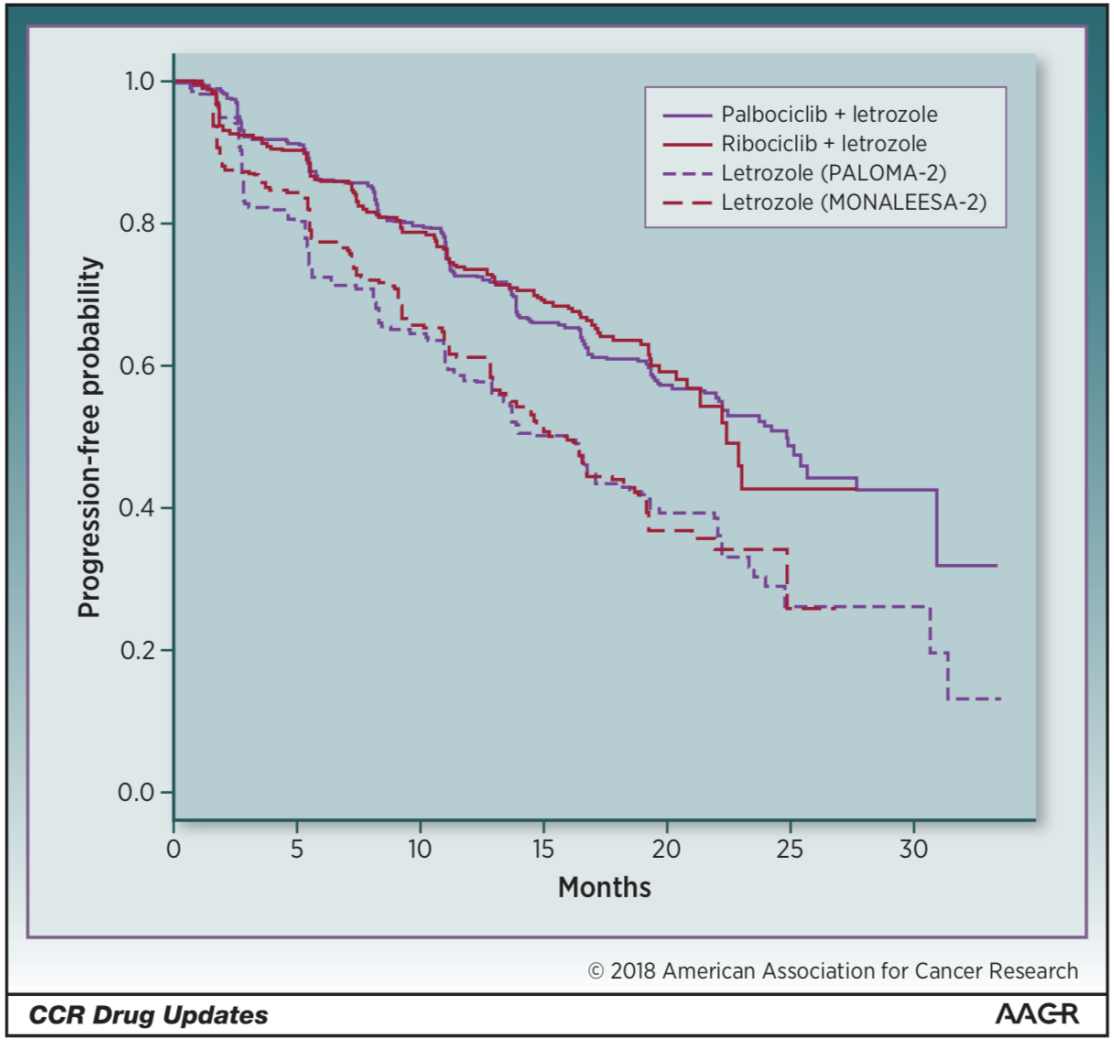
ORR: 59.2%

1) Finn et al. NEJM 2016
2) Hortobagyi et al. NEJM 2016
3) Goetz et al. JCO 2017

Presented By Matthew Goetz at 2018 ASCO Annual Meeting

MONALEESA-2 (Ribociclib + Letrozole) and PALOMA-2 (Palbociclib + Letrozole)

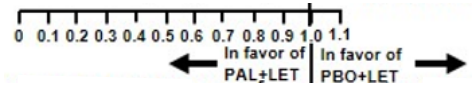
“Cross-study inferences should not be made.”



Shah A, et al. Clin Cancer Res. 2018 [Epub ahead of print].

PALOMA-2 Efficacy – Patient Subgroups

Baseline Factors	PAL+LET Patients, n (%)	PBO+LET Patients, n (%)	PAL+LET mPFS (95% CI)	PBO+LET mPFS (95% CI)	PAL+LET vs PBO+LET HR (95% CI)	*P**
All randomized patients, IA	444 (100)	222 (100)	27.6 (22.4-30.3)	14.5 (12.3-17.1)	0.56 (0.46-0.69)	<.0001
All randomized patients, BICR	444 (100)	222 (100)	35.7 (27.7-38.9)	19.5 (16.6-26.6)	0.61 (0.49-0.77)	<.0001
Visceral disease	214 (48.2)	110 (49.5)	19.3 (16.4-24.2)	12.3 (8.4-16.4)	0.62 (0.47-0.81)	<.0005
Nonvisceral disease	230 (51.8)	112 (50.5)	35.9 (27.7-NE)	17.0 (13.8-24.8)	0.50 (0.37-0.67)	<.0001
Bone-only disease	103 (23.2)	48 (21.6)	36.2 (27.6-NE)	11.2 (8.2-22.0)	0.41 (0.26-0.63)	<.0001
No bone-only disease[b]	341 (76.8)	174 (78.4)	24.2 (19.4-27.7)	14.5 (12.9-18.5)	0.62 (0.50-0.78)	<.0001
DFI[†]>12 mo	179 (40.3)	93 (41.9)	30.3 (24.8-NE)	13.8 (8.8-18.2)	0.55 (0.40-0.76)	<.0005
DFI[†]≤12 mo	98 (22.1)	48 (21.6)	16.6 (13.9-24.2)	11.0 (5.6-12.9)	0.48 (0.32-0.72)	<.0005
DFI[†]>2 y	154 (34.7)	77 (34.7)	38.5 (27.5-NE)	16.6 (13.7-23.5)	0.52 (0.36-0.75)	<.0005
DFI[†]>5 y	90 (20.3)	46 (20.7)	38.6 (27.6-NE)	23.5 (16.3-32.2)	0.60 (0.36-1.00)	<.05
DFI[†]>10 y	32 (7.2)	23 (10.4)	NR (30.4-NE)	23.5 (16.6-NE)	0.44 (0.19-1.03)	<.05
De novo metastatic	167 (37.6)	81 (36.5)	27.9 (22.1-33.4)	22.0 (13.9-27.4)	0.61 (0.44-0.85)	<.005
DFI from prior ET >12 mo	156 (35.1)	78 (35.1)	27.6 (22.2-38.6)	13.8 (8.2-16.6)	0.58 (0.41-0.82)	<.001
DFI from prior ET ≤12 mo	94 (21.2)	48 (21.6)	16.6 (13.9-24.2)	11.0 (5.6-12.9)	0.49 (0.33-0.73)	<.0005
Measurable disease	338 (76.1)	171 (77.0)	23.7 (19.3-27.6)	14.5 (12.3-18.5)	0.63 (0.50-0.79)	<.0001
Nonmeasurable disease[§]	106 (23.9)	51 (23.0)	36.2 (27.6-NE)	16.5 (8.3-19.6)	0.39 (0.25-0.60)	<.0001
No prior ET with visceral disease	86 (19.4)	47 (21.2)	23.7 (16.8-30.3)	13.9 (10.2-22.2)	0.55 (0.36-0.85)	<.005
No prior ET w/o visceral disease	108 (24.3)	49 (22.1)	36.2 (27.9-NE)	27.6 (19.1-35.6)	0.59 (0.38-0.92)	<.01
Prior ET	250 (56.3)	126 (56.8)	24.2 (18.8-27.6)	11.2 (8.4-14.5)	0.54 (0.42-0.71)	<.0001
No prior ET	194 (43.7)	96 (43.2)	30.3 (24.5-35.7)	21.9 (15.9-27.4)	0.59 (0.43-0.80)	<.0005
Prior chemotherapy	213 (48.0)	109 (49.1)	24.8 (19.3-27.9)	12.9 (9.6-16.5)	0.53 (0.40-0.71)	<.0001
No prior chemotherapy	231 (52.0)	113 (50.9)	27.9 (23.2-33.4)	18.5 (13.6-24.8)	0.59 (0.45-0.79)	<.0005
Disease site, 1	138 (31.1)	66 (297)	30.4 (24.8-NE)	16.5 (11.0-22.1)	0.52 (0.36-0.75)	<.0005
Disease site, 2	117 (26.4)	52 (23.4)	28.1 (19.4-NE)	16.3 (11.0-27.4)	0.57 (0.37-0.89)	<.01
Disease site, ≥3	189 (42.6)	104 (46.8)	23.7 (19.2-27.6)	13.8 (8.8-17.0)	0.61 (0.46-0.82)	<.0005
ECOG PS 0	257 (57.9)	102 (45.9)	27.9 (24.9-36.2)	19.3 (14.5-24.9)	0.65 (0.48-0.87)	<.005
ECOG PS 1/2	187 (42.1)	120 (54.1)	22.2 (16.6-27.7)	11.8 (8.3-16.5)	0.51 (0.39-0.68)	<.0001
Age <65 y	263 (59.2)	141 (63.5)	23.2 (19.3-27.6)	13.7 (11.0-16.6)	0.55 (0.43-0.70)	<.0001
Age ≥65 y	181 (40.8)	81 (36.5)	30.6 (27.6-NE)	19.1 (11.0-30.4)	0.60 (0.43-0.86)	<.005



*1-sided *P* value from the log-rank test
[b]Per tumor site
[†]Protocol-defined DFI refers to DFI since completion of prior (neoadjuvant therapy and onset of metastatic disease or disease recurrence)
[§]A few patients initially enrolled as having measurable disease were later found to have nonmeasurable disease beyond bone-only disease

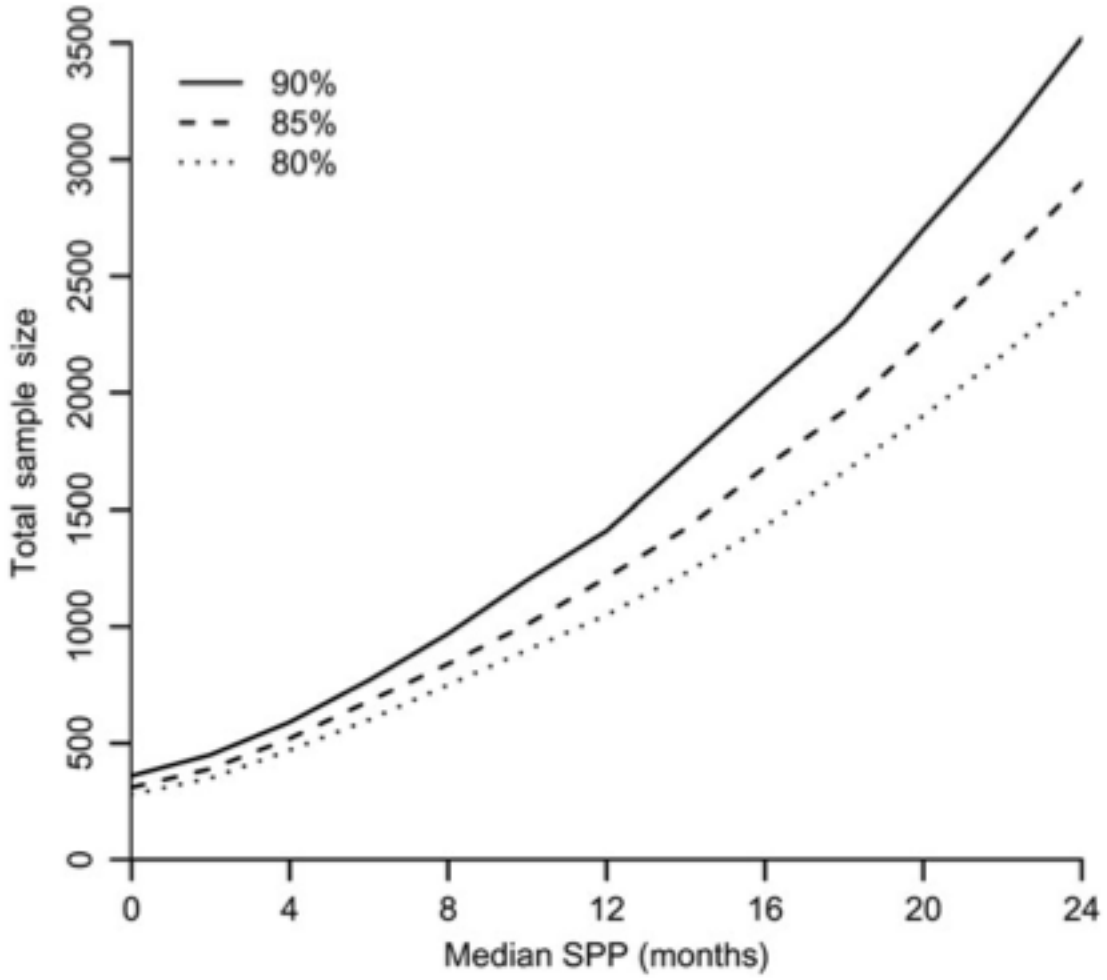
Rugo HS, et al. Presented at: 2017 San Antonio Breast Cancer Symposium; December 5-9, 2017; San Antonio, Texas. Abstract P5-21-03.

Summary of Biomarker Data

- ***De Novo* Resistance**
  - Preclinical and clinical data that *CCNE1* (Cyclin E) associated with poor survival and CDK 4/6i resistance
  - FGFR amplification associated with resistance to endocrine therapy and CDK 4/6i
- **Acquired Resistance**
  - Preliminary evidence for acquired *Rb1* mutations at time of progression (frequency low)
  - Do ER+ cancer cells retain endocrine sensitivity after progression on CDK 4/6 inhibitor?
  - The majority of mechanisms for acquired resistance are unknown

1) Keyomarsi et al. NEJM 2002
2) Turner et al AACR 2018
3) Formisiano SABC 2017
3) Condorelli Annals of Oncology 2018
4) Turner et al. ASCO 2018

Sample Sizes Required for Detecting a Statistically Significant Difference in Overall Survival by Median Survival Post Progression (SPP)



Broglio KR, Berry DA. J Natl Cancer Inst. 2009;101(23):1642-1649.

npj | Breast Cancer

www.nature.com/npjbcancer

PERSPECTIVE OPEN

Cdk4/6 inhibitors and overall survival: power of first-line trials in metastatic breast cancer

Marie-Laure Tanguy[1], Luc Cabel[2,3], Fréderique Berger[1], Jean-Yves Pierga[2,4], Alexia Savignoni[1] and Francois-Clement Bidard[2,3]

PALOMA-2 and MONALEESA trials have an almost similar power despite different allocation ratios, while MONARCH-3 has a more limited power. Overall, the power of these trials to demonstrate a statistically significant improvement in OS is less than 70% if the prolongation in median OS is ≤12 months, whatever the OS data maturity. This analysis shows that OS results are jeopardized by limited powers, and a meta-analysis might be required to demonstrate OS benefit.

Tanguy, et al., npj Breast Cancer (2018)4:14

Pfizer Announces Overall Survival Results from Phase 3 PALOMA-3 Trial of IBRANCE® (Palbociclib) in HR+, HER2- Metastatic Breast Cancer

- *Results show a positive trend in the secondary endpoint of overall survival, though not reaching statistical significance*
- *IBRANCE is approved worldwide in combination with fulvestrant based on compelling results from the primary endpoint of progression-free survival*

Monday, June 25, 2018 8:00 am EDT

Dateline:
NEW YORK

Public Company Information:

NYSE: PFE
US7170811035

NEW YORK--(BUSINESS WIRE)--Pfizer today announced overall survival (OS) results from the Phase 3 PALOMA-3 trial, which evaluated IBRANCE® (palbociclib) in combination with fulvestrant compared to placebo plus fulvestrant in women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer whose disease has progressed after prior endocrine therapy. The results demonstrated a positive trend in the hazard ratio favoring the IBRANCE combination, although this trend did not reach statistical significance. Overall survival is a secondary endpoint of the PALOMA-3 trial and, as such, the trial design was not optimized to detect a statistically significant difference in OS.

"The duration of the survival in hormone receptor-positive metastatic breast cancer patients, and the potential for subsequent therapies to confound overall survival outcomes,

Endocrine Therapy of Breast Cancer -- Messages:

- Recurrence/Resistance after endocrine therapy for breast cancer represents a substantial unmet need.
- PIK3CA mutations appear to be predictive factors for p110a catalytic isoform-specific inhibitors.
- The identification of appropriate biomarkers of efficacy and the development of optimal combination therapies and dosing schedules for PI3Kis are likely to be required for the graduation of this class of compounds to clinical practice.
- CDK4/6 inhibitors improve the durability of both first and second-line endocrine responses in patients with metastatic, HR+ breast cancer.
- No biomarkers have yet been identified to select patients who are most likely to respond to CDK4/6 inhibition.


Questions/Comments
Discussion
Criticism
Debate
James H. Clark Center
Stanford University
Stanford Bio-X Program:
Biology, Medicine, Chemistry,
Physics and Engineering