IO SONO QUI

SAVERIO CINIERI

UNITÀ OPERATIVA COMPLESSA
ONCOLOGIA MEDICA & BREAST UNIT BRINDISI
& MED ONCOLOGY DPT EUROPEAN INSTITUTE
OF ONCOLOGY, MILANO

& IRCSG
& UNIVERSITÀ DEGLI STUDI DI BARI
& UNIVERSITÀ DEGLI STUDI DEL SALENTO

Saverio Cinieri Disclosures

Direct and indirect with OncologyPharma Companies:

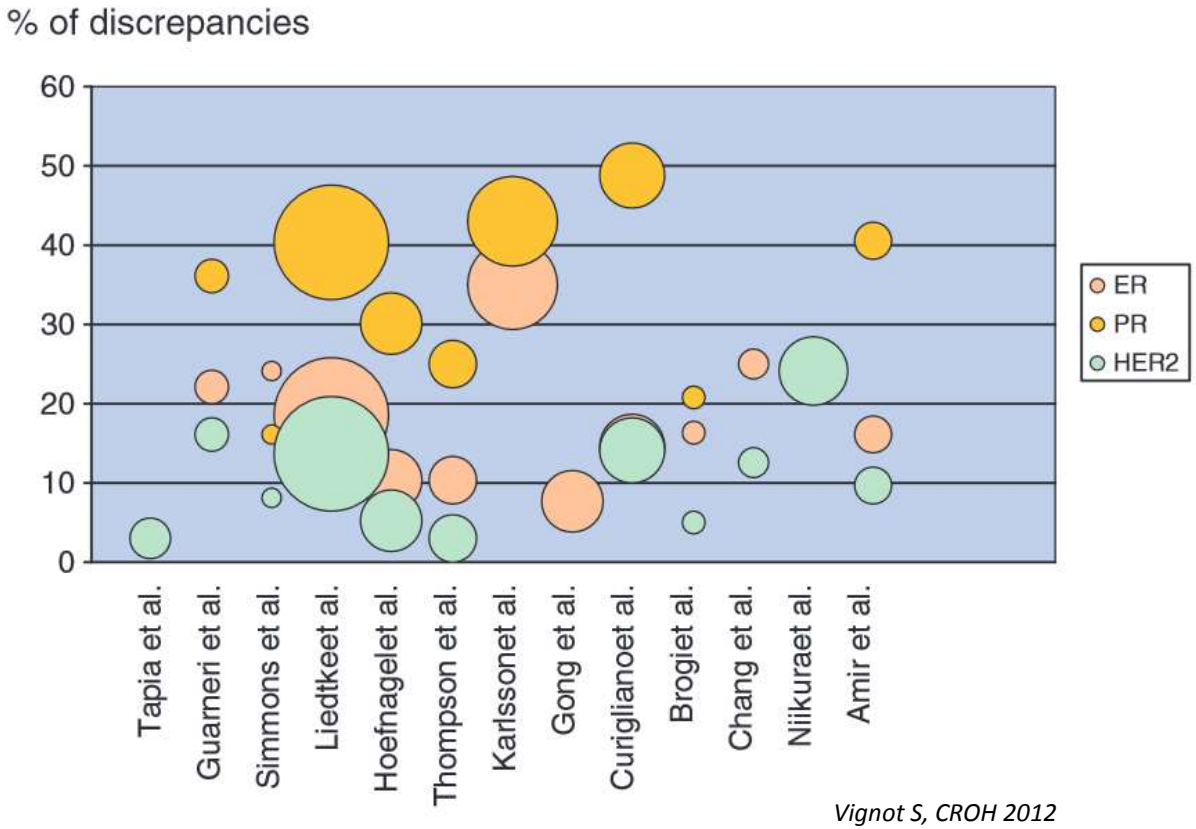
Honoraria, Institutional Grants/Research Support, Advisory Boards, Scientific National and International Meeting Support.

Lilly, Pfizer, Roche, AstraZeneca, Amgen, Novartis, Pierre Fabre, Italfarmaco, Astellas, Takeda, Eisai, Bayer, Teva, Boehringer Ingelheim, Servier, Sanofi Genzyme, MSD, Merk Serono, Celgene, BMS, Ipsen, Puma, Incyte, Pierrefabre.

These relantionships do not impact my ability to present an unbiased presentation.

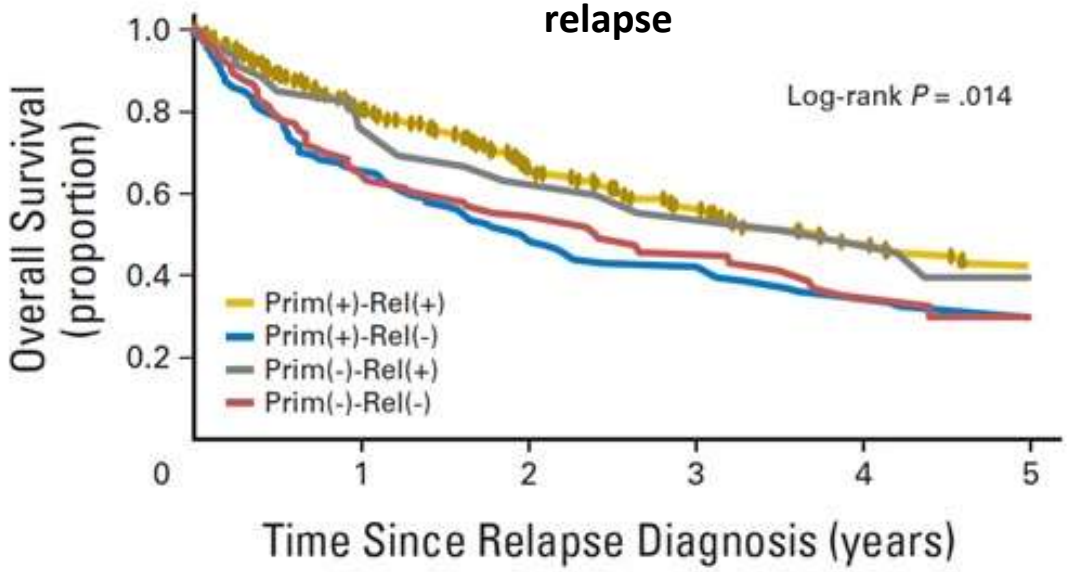
Biology of HR+/HER2- MBC

Receptor status may change during metastatic progression and receptor discordance can have a prognostic impact.



Vignot S, CROH 2012

Intraindividual ER status in primary tumor and in relapse

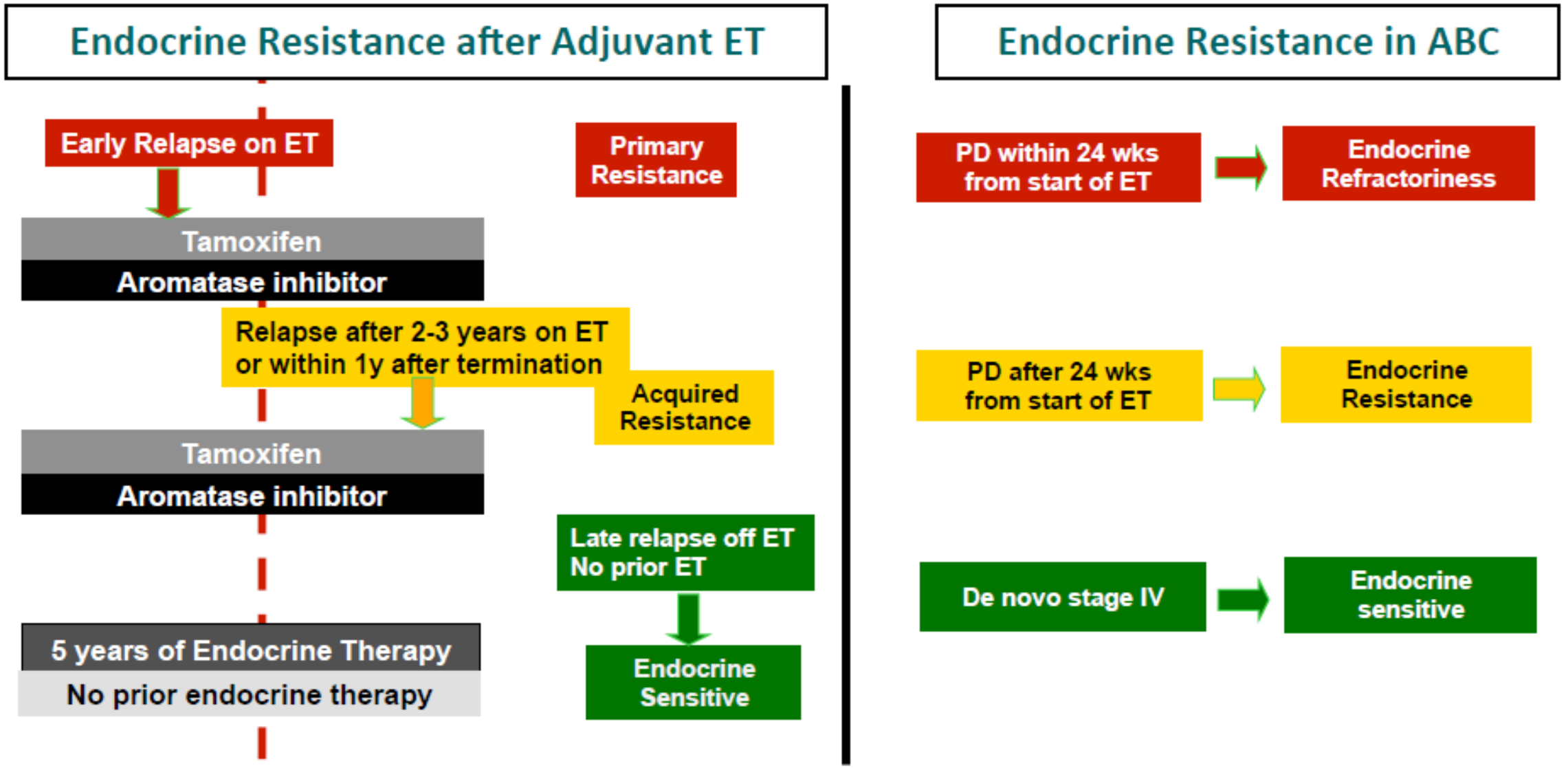


Lindström LS, J Clin Oncol 2012

Endocrine Therapy for HR+ MBC: key considerations

- Sequential hormone therapy is the preferential treatment for most patients with HR-positive/HER2-negative MBC.
- Many treatment options available: endocrine monotherapy or combinations with targeted agents.
- Endocrine resistance is universal, duration of response is variable.
- Chemotherapy as first line should be considered for patients with immediately life-threatening disease.

Endocrine Resistance

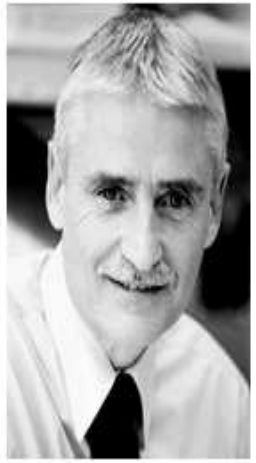


Modified from S Johnston and ABC3

The Nobel Prize in Physiology or Medicine 2001

Leland Hartwell, Tim Hunt, Sir Paul Nurse

The Nobel Prize in Physiology or Medicine 2001



Leland H. Hartwell
Prize share: 1/3

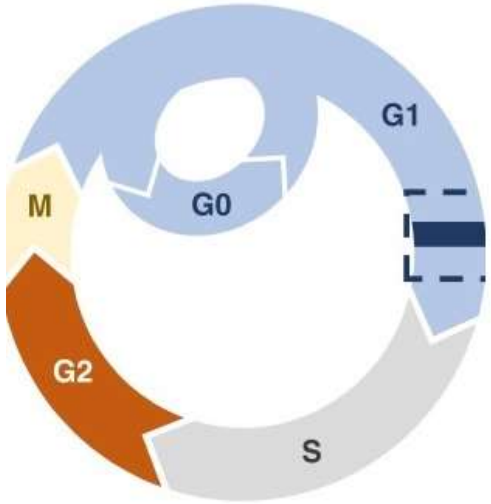
Tim Hunt
Prize share: 1/3

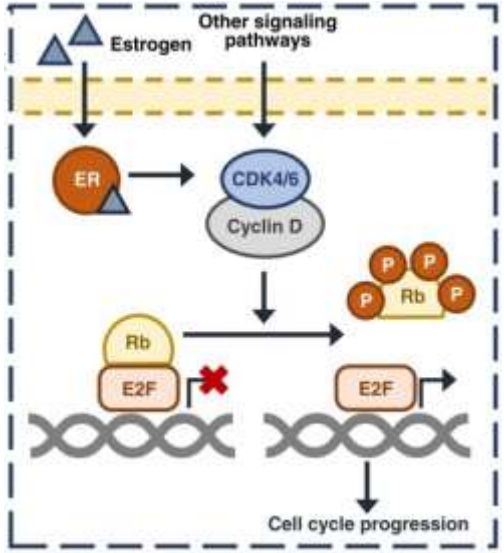
Sir Paul M. Nurse
Prize share: 1/3

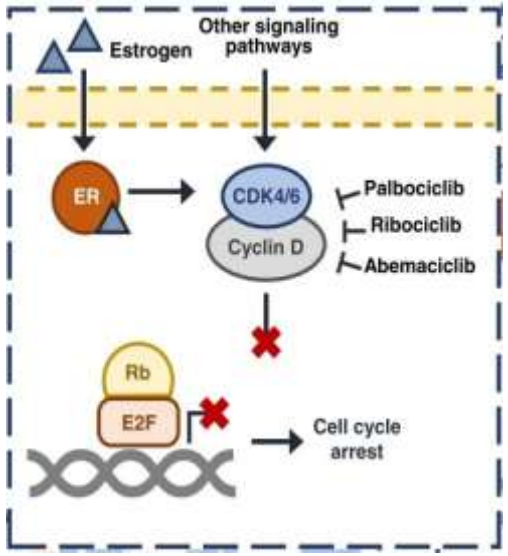
The Nobel Prize in Physiology or Medicine 2001 was awarded jointly to Leland H. Hartwell, Tim Hunt and Sir Paul M. Nurse *"for their discoveries of key regulators of the cell cycle"*.

Work in yeast led to Nobel prize in 2001:
Nurse, Hartwell and Hunt for discovery of CDKs

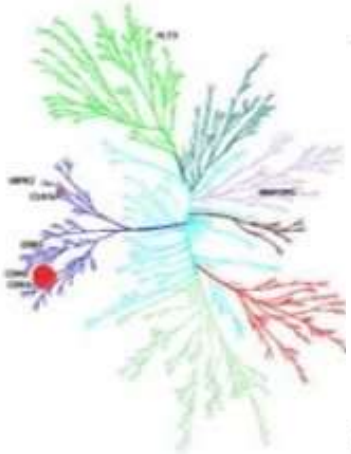
CDK 4/6 inhibitors

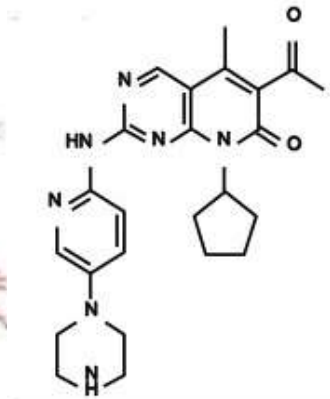






Sammons SL et al, Curr Cancer Drug Target 2017





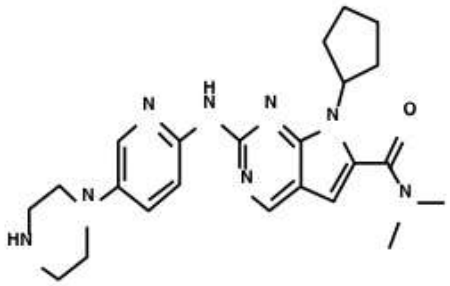
Palbociclib

CDK4 IC_{50} = 11 nM
CDK6 IC_{50} = 16 nM

FDA approved 2015

Ribociclib

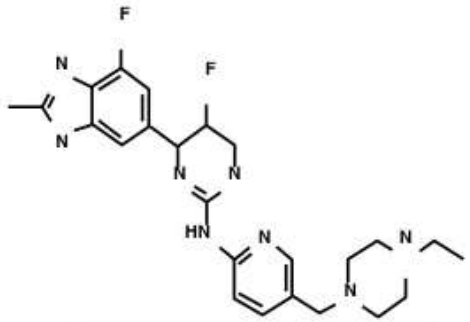
Selectivity
- 1×
- 10×
- 100×



CDK4 IC_{50} = 10 nM
CDK6 IC_{50} = 39 nM

FDA approved 2017

Abemaciclib



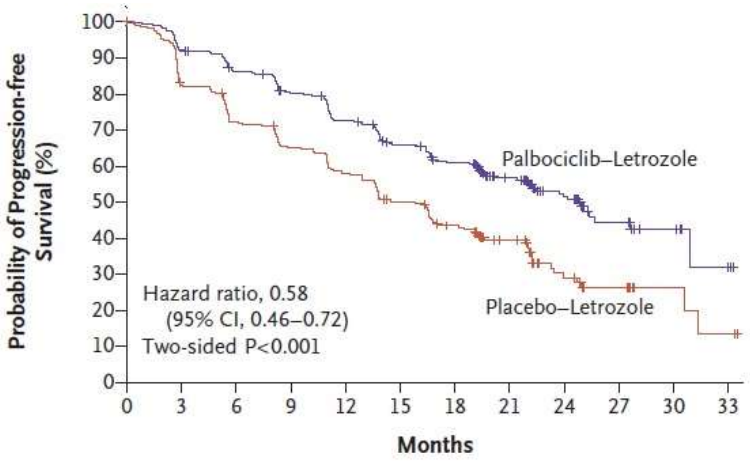
CDK4 IC_{50} = 2 nM
CDK6 IC_{50} = 9.9 nM
CDK9 IC_{50} = 57 nM
CDK1 IC_{50} = 1,627 nM

FDA approved 2017

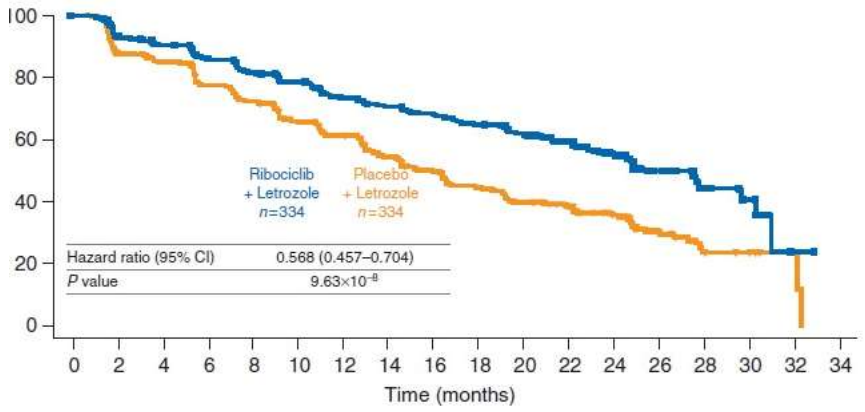
l, Mol Can Ther, 2016

CDK 4/6 inhibitors: first line setting

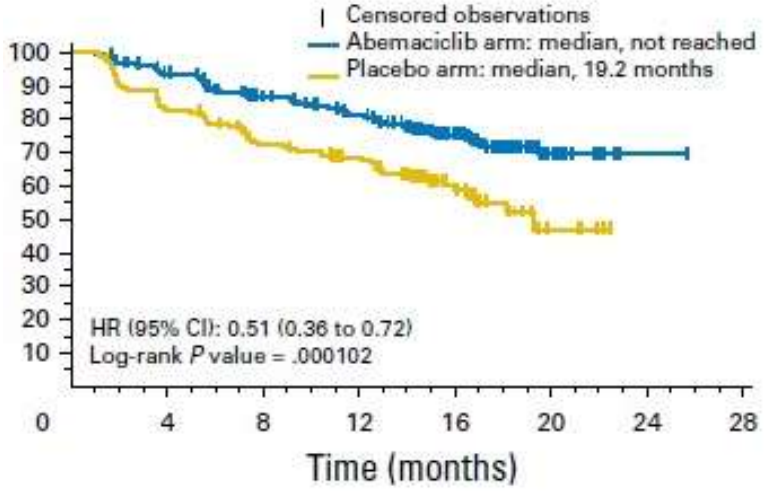
First-line, AI-sensitive	n	Treatment	PFS CDK4/6	PFS Placebo	HR (95%CI)
PALOMA-2	666	Let+Palbo Let+Pla	24.8	14.5	0.58 (0.46-0.72)
MONALEESA-2	668	Let+Ribo Let+Pla	25.3	16.0	0.57 (0.46-0.70)
MONARCH-3	493	AI+Abema AI+Pla	28.8	14.8	0.54 (0.42-0.70)



Finn RS et al , N Engl J Med, 2016



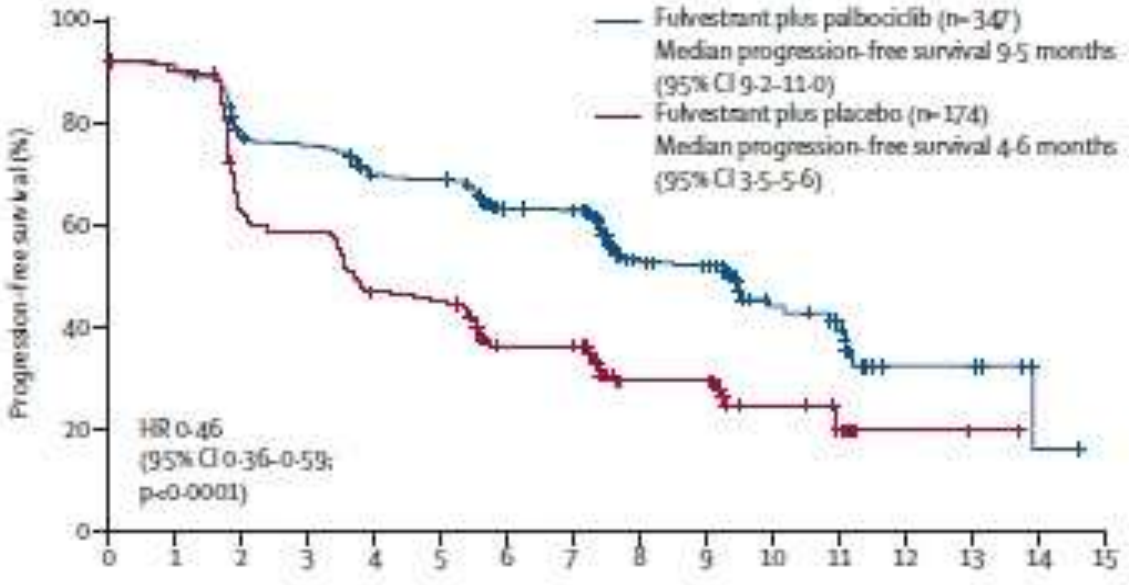
Hortobagyi GN et al , Ann Oncol 2018



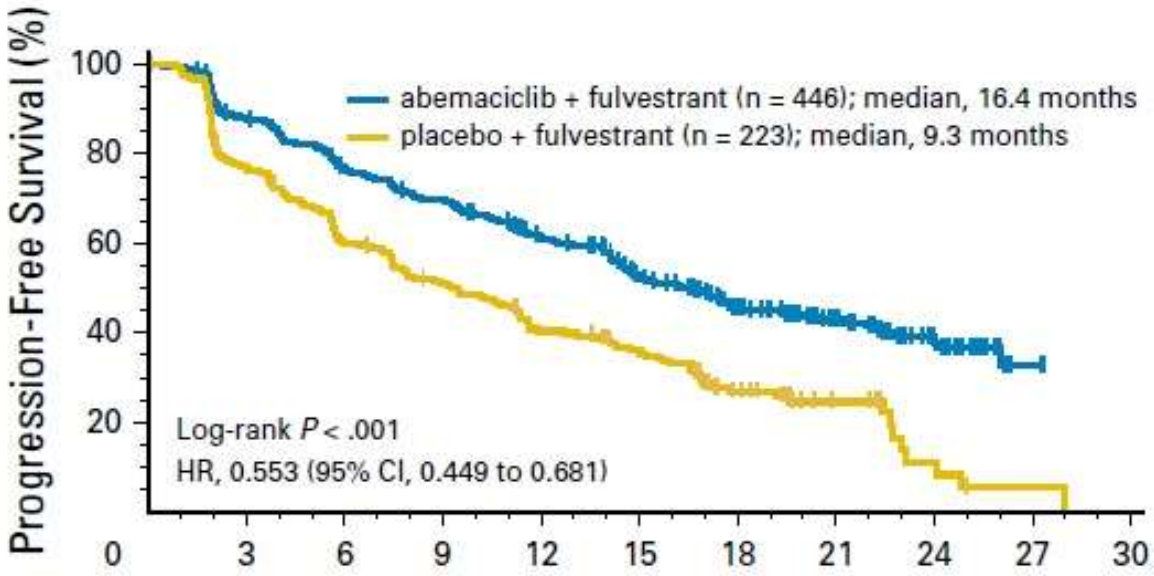
Goetz et al, J Clin Oncol, 2017

CDK 4/6 inhibitors:
2nd line or early relapse during/after adjuvant ET

Second-line, endocrine pretreated	n	Treatment	PFS CDK 4/6	PFS Placebo	HR (95%CI)
PALOMA-3	521	Fulv+Palbo Fulv+Plac	9.5	4.6	0·46 (0·36–0·59)
MONARCH-2	669	Fulv+Abema Fulv+Pla	16.4	9.3	0.55 (0.45-0.68)

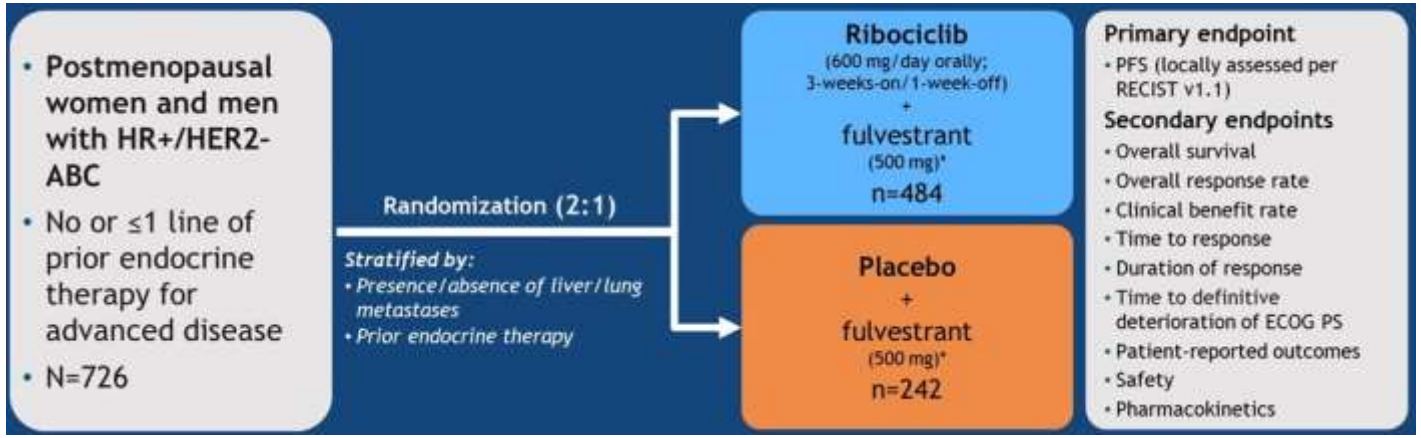


Cristofanilli M. et al , Lancet Oncol 2016

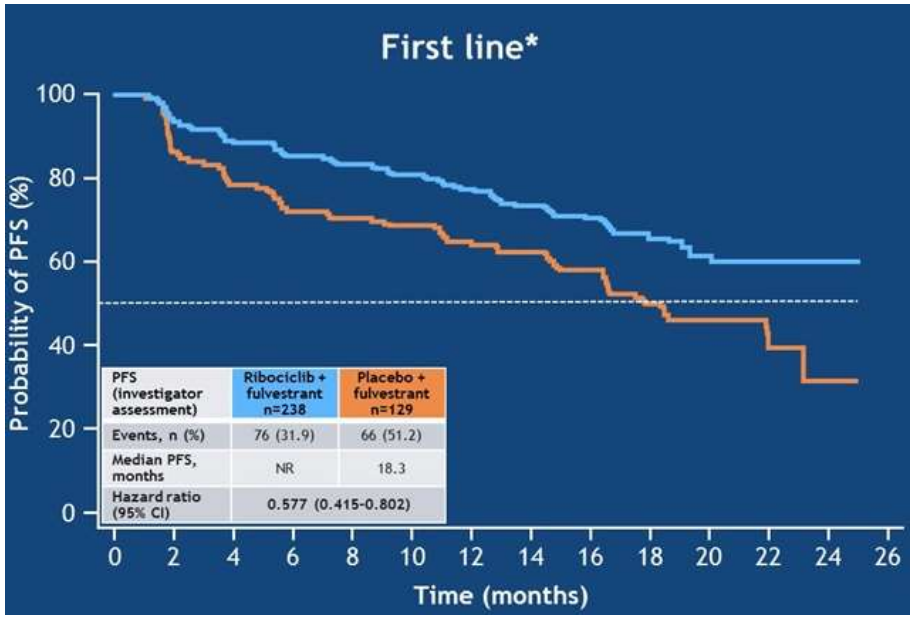


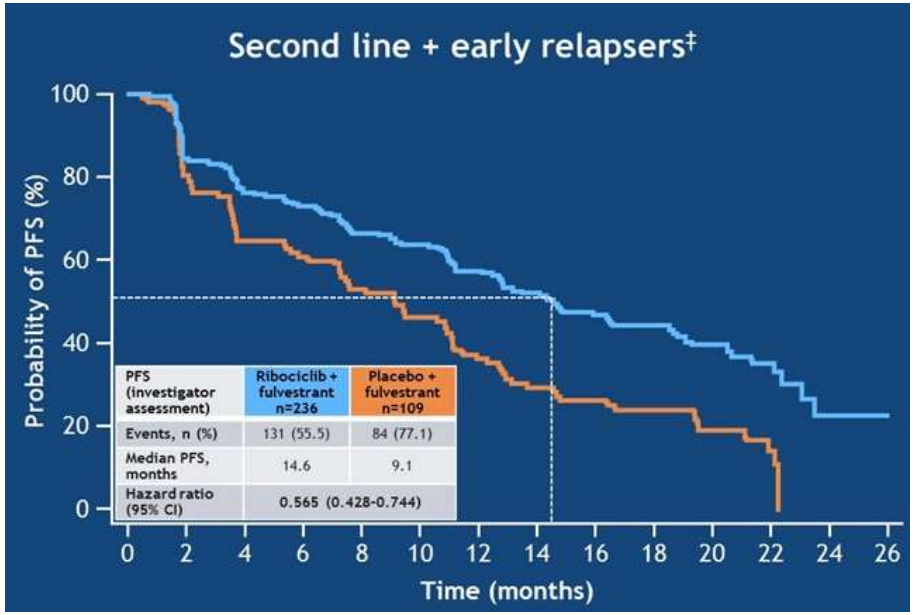
Sledge GW et al, J Clin Oncol 2017

MONALEESA-3: phase III placebo-controlled study of ribociclib + Fulv



First line *(i.e. treatment-naive for ABC)*	Second line + early relapsers *(i.e. received up to 1 line of prior endocrine therapy for ABC)*
• **Relapse** >12 months after completion of (neo)adjuvant endocrine therapy OR • *De novo* advanced/metastatic disease (no prior exposure to endocrine therapy)	• **Early relapse** on or ≤12 months from completion of (neo)adjuvant endocrine therapy OR • **Relapse** >12 months from completion of (neo)adjuvant endocrine therapy with subsequent **progression** after 1 line of endocrine therapy (antiestrogen/AI) for ABC OR • ABC at diagnosis that **progressed** after 1 line of endocrine therapy (antiestrogen/AI) for ABC





Slamon DJ ASCO 2018

CDK 4/6 inhibitors: place in therapy

Drug	Trial	1st CDK4/6 + AI PFS mo	Trial	2nd Fulv PFS mo	TOT mPFS
Palbociclib	**PALOMA-2**	27.6	**PALOMA-3**	4.6*	**32.2**
Abemaciclib	**MONARCH-3**	28.8	**MONARCH-2**	9.3	**38.1**
Ribociclib	**MONALEESA-2**	25.3	**MONALEESA-3**	9.2	**34.5**
Drug	**Trial**	**1st AI PFS mo**	**Trial**	**2nd Fulv+CDK4/6inh PFS mo**	**TOT mPFS**
Palbociclib	**PALOMA-2**	14.5	**PALOMA-3**	11.2*	**25.7**
Abemaciclib	**MONARCH-3**	14.8	**MONARCH-2**	16.4	**31.2**
Ribociclib	**MONALEESA-2**	16.0	**MONALEESA-3**	14.6	**30.6**

*heavily pretreated

CDK 4/6 inhibitors: place in therapy

CDK4/6i upfront for all?

- OS data
- Clinical subgroups
- Toxicity
- Quality of life
- Costs
- Regulatory restrictions (still no data on CDK4/6i after 1st line fulvestrant)
- Biomarkers

CDK 4/6 inhibitors: overall survival

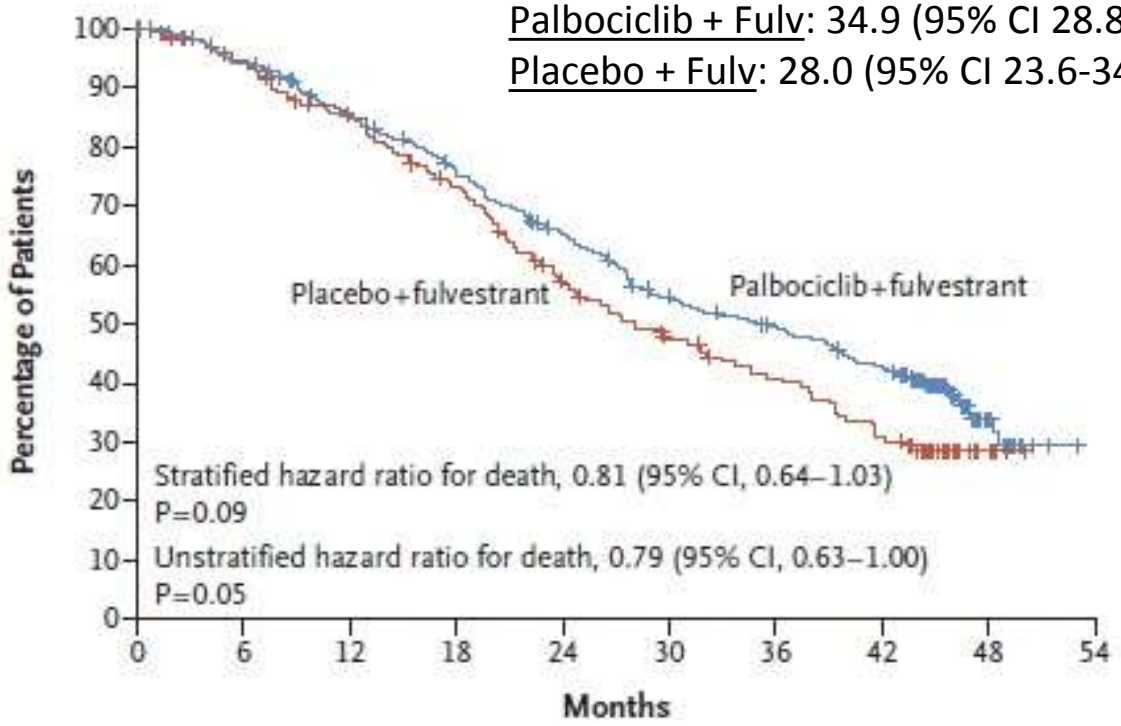
ORIGINAL ARTICLE

Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer

N.C. Turner, D.J. Slamon, J. Ro, I. Bondarenko, S.-A. Im, N. Masuda, M. Colleoni, A. DeMichele, S. Loi, S. Verma, H. Iwata, N. Harbeck, S. Loibl, F. André, K. Puyana Theall, X. Huang, C. Giorgetti, C. Huang Bartlett, and M. Cristofanilli

Presented at ESMO 2018

Median OS months
Palbociclib + Fulv: 34.9 (95% CI 28.8-40.0)
Placebo + Fulv: 28.0 (95% CI 23.6-34.6)



CDK 4/6 inhibitors: overall survival

LONG NATURAL HYSTORY OF DISEASE

- Impact of new therapy at early point
- Impact of subsequent therapy
- Trials not powered for OS
- Individual patient-level meta-analysis

CDK 4/6 inhibitors: post-progression data

PALOMA-3

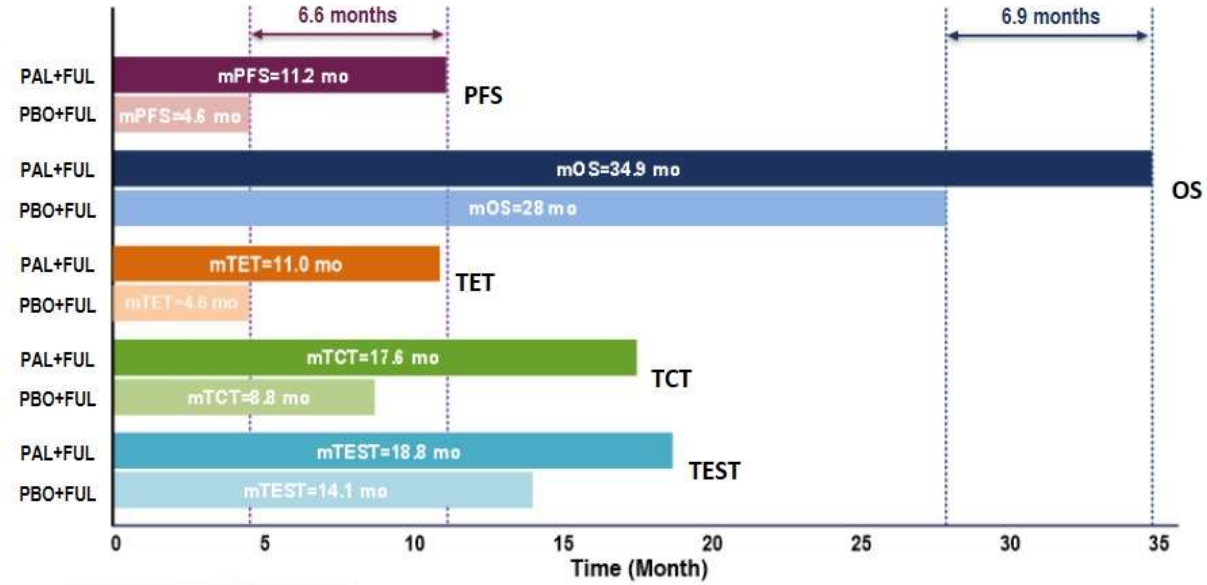
SYSTEMIC SUBSEQUENT ANTICANCER THERAPIES

	Palbociclib + Fulvestrant (n=347)			Placebo + Fulvestrant (n=174)		
	Line of Subsequent Therapy					
Treatment, n (%)*	First	Second	Third or Greater	First	Second	Third or Greater
Any treatment received†	248	182	131	140	113	85
Chemotherapy	138 (56)	133 (73)	121 (92)	87 (62)	76 (67)	76 (89)
Antihormonal	100 (40)	40 (22)	38 (29)	52 (37)	29 (26)	31 (36)
mTOR kinase inhibitor	40 (16)	17 (9)	20 (15)	21 (15)	12 (11)	13 (15)
CDK4/6 inhibitors‡	6 (2)	2 (1)	6 (5)	9 (6)	6 (5)	15 (18)

Median (range) number of lines of post-progression therapy: palbociclib arm, 2 (1-10); placebo arm, 3 (1-10).

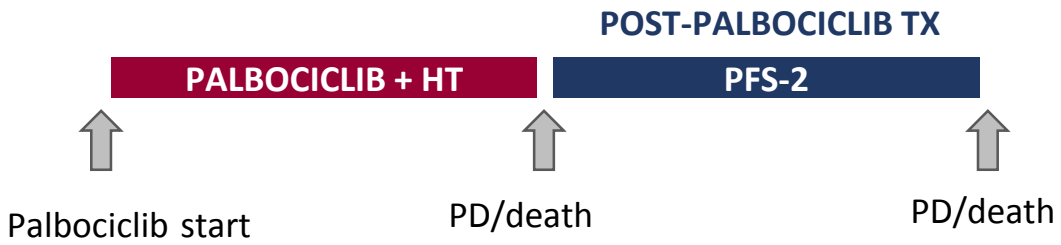
27 patients in the PBO arm received postprogression CDK4/6 inhibitor treatment.

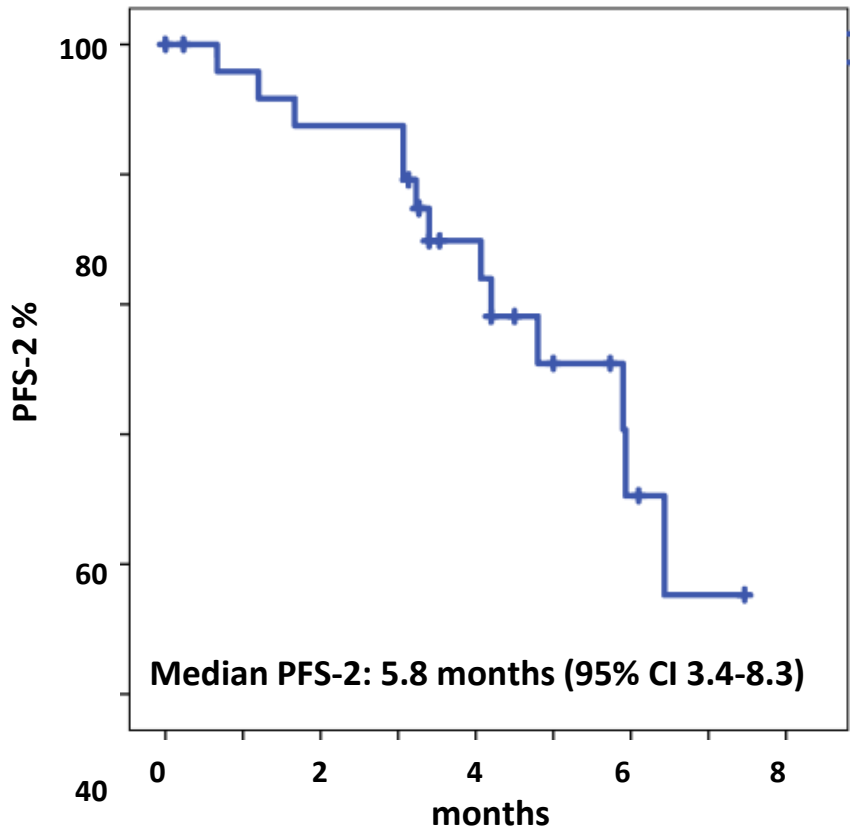
- Sensitivity analysis suggests reduction of the treatment effect size



Cristofanilli M, ESMO 2018

CDK 4/6 inhibitors: real-world data





Treatment post-palbociclib	Frequency (%)
Systemic anticancer treatment	26 (76.5)
Chemotherapy	24 (92.3)
Caelyx	4 (15.4)
Capecitabine	7 (26.9)
Carboplatin + Gemcitabine	1 (3.8)
Eribuline	6 (23.1)
Nab-paclitaxel	5 (19.3)
MTX – Ciclophosphamide	1 (3.8)
Endocrine Therapy	2 (7.7)
Everolimus + Exemestane	2 (7.7)
Best Supportive Care	8 (23.5)

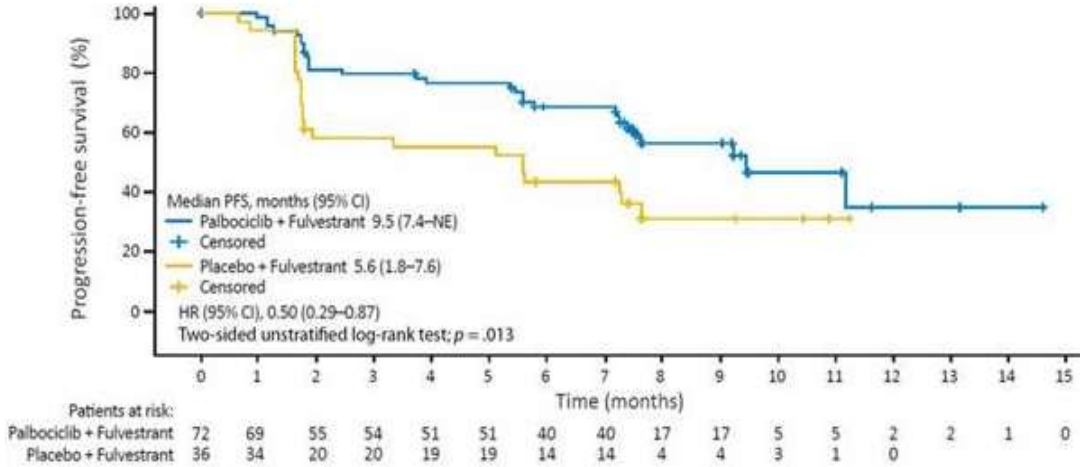
Best Response	Frequency (%)
CR	0 (0.0)
PR	1 (4.2)
SD	15 (62.5)
PD	8 (33.3)

Menichetti A, AIOM giovani 2018

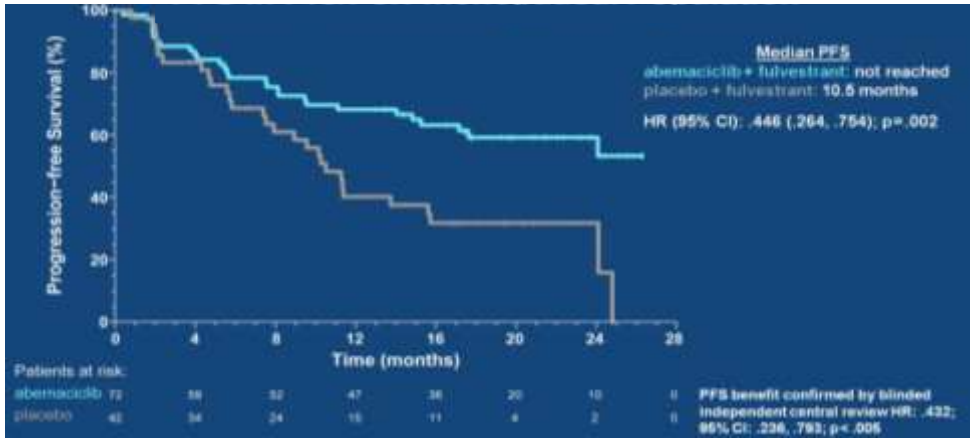
CDK 4/6 inhibitors: clinical subgroups

Fulvestrant + CDK 4/6 inhibitors in premenopausal women

PALOMA-3 (subgroup analysis)



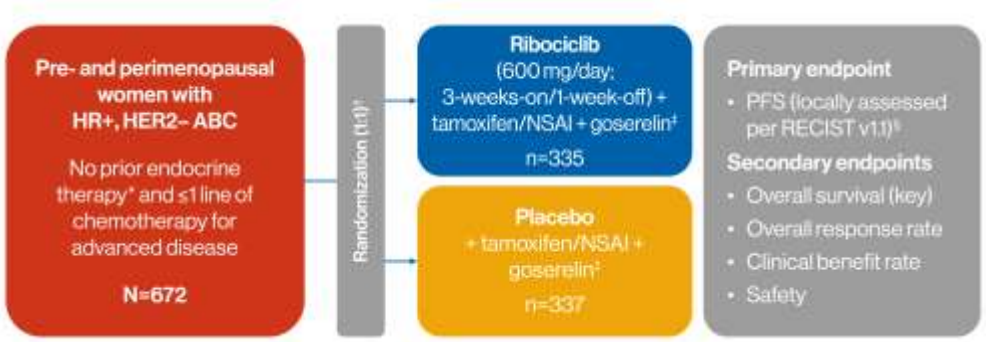
MONARCH-2 (subgroup analysis)

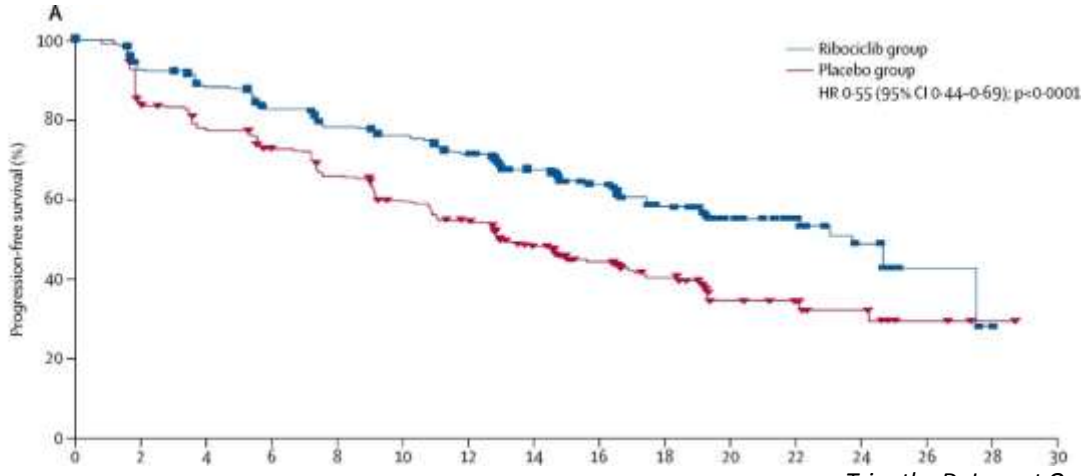


Loibl S, Oncologist 2017; Neven P, ASCO 2018

AI/tamoxifen + goserelin + CDK 4/6 inhibitors in premenopausal women

MONALEESA-7



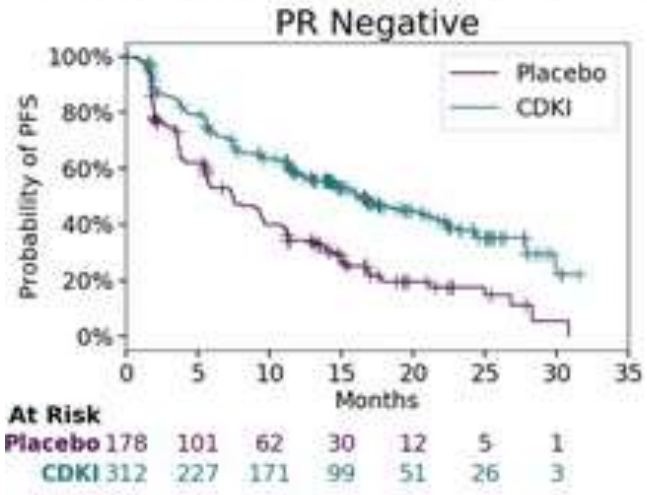


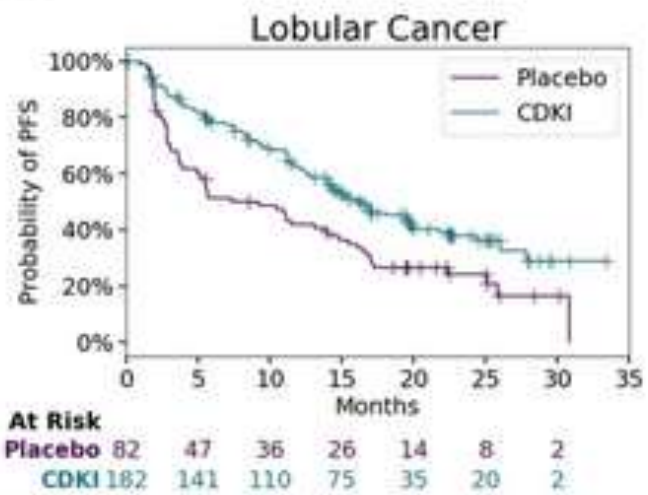
Tripathy D, Lancet Oncol 2018

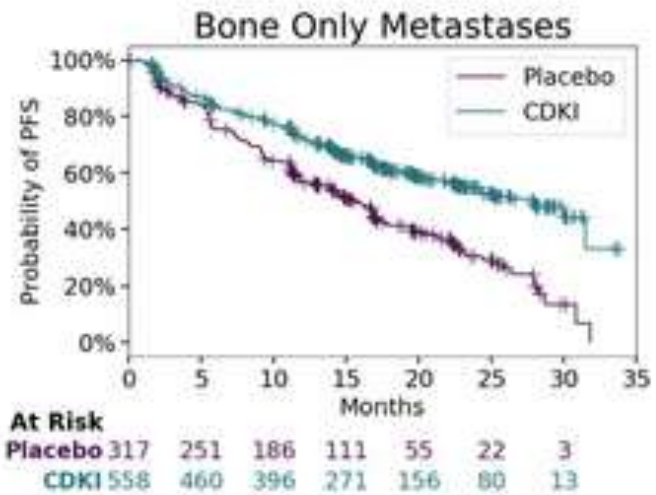
CDK 4/6 inhibitors: clinical subgroups

FDA pooled analysis of raw data from 5 RCTs: PALOMA-2, PALOMA-3, MONALEESA-2, MONARCH-2, MONARCH-3

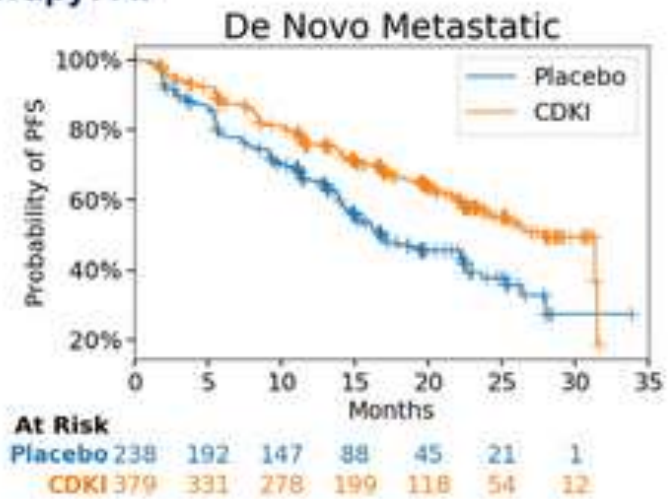
Endocrine Therapy: AI or Fulvestrant

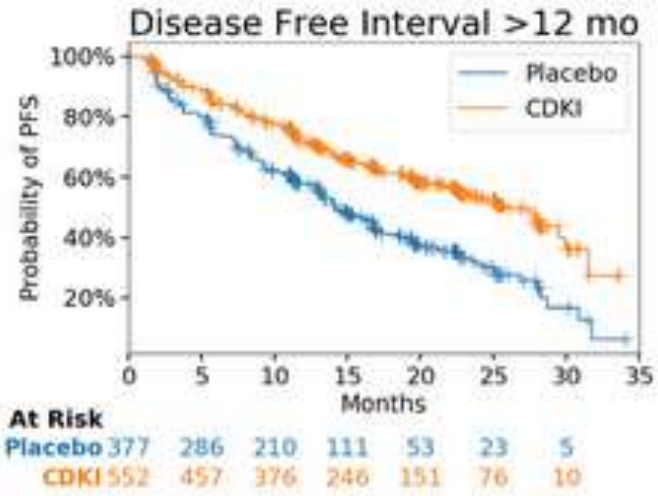






Endocrine Therapy: AI



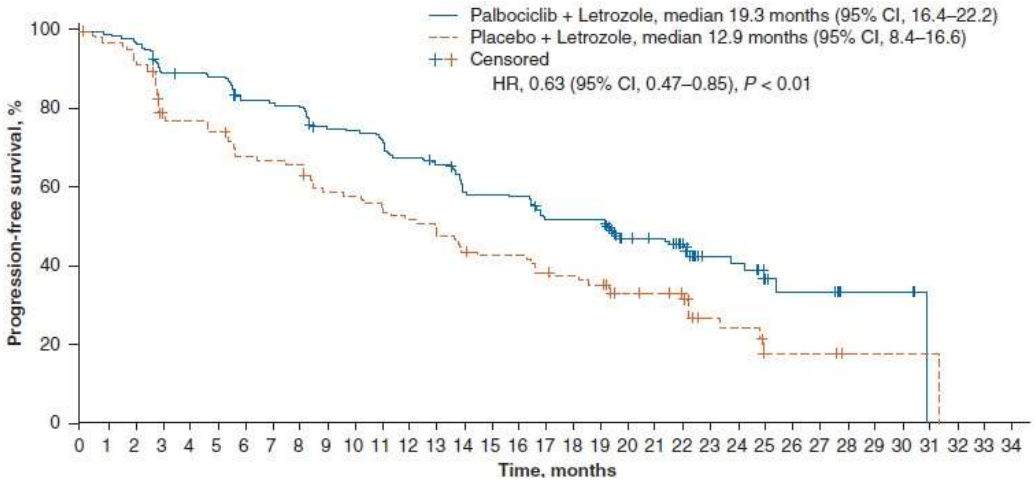


Gao J, ASCO 2018

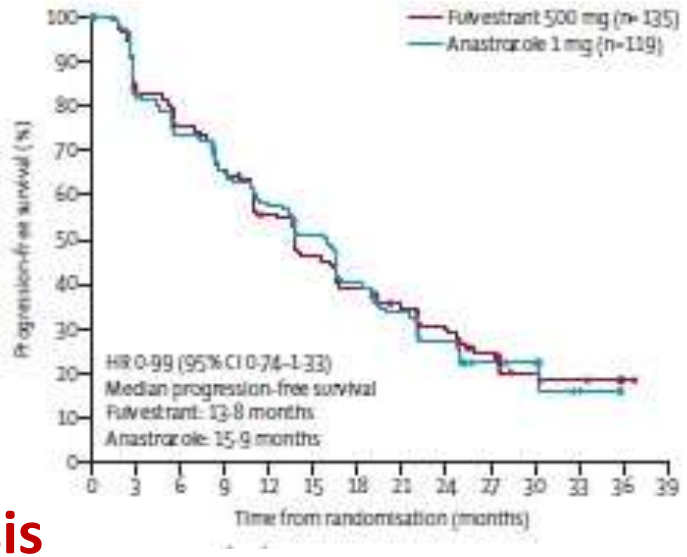
CDK 4/6 inhibitors: clinical subgroups

Pts with visceral metastasis

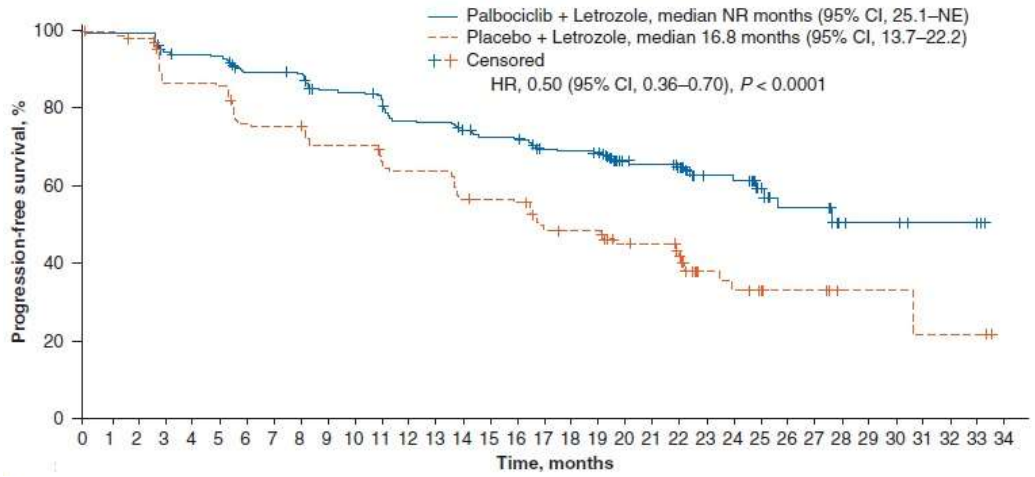
PALOMA-2

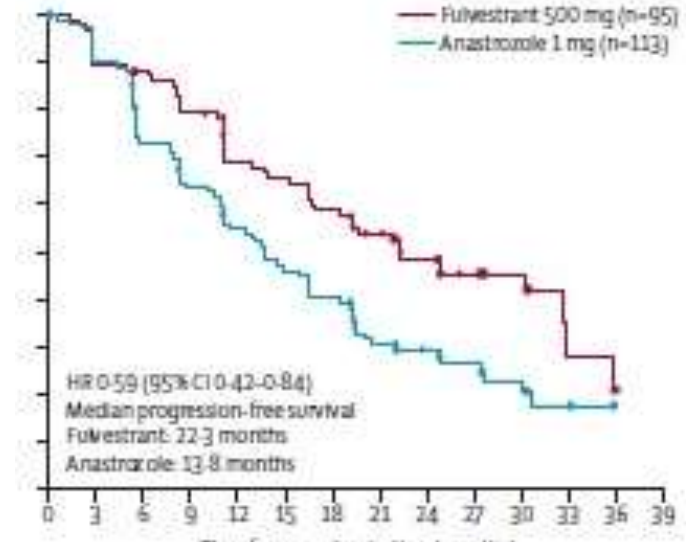


FALCON



Pts without visceral metastasis





Turner NC et al, Ann Oncol 2018

Robertson J et al, Lancet 2016

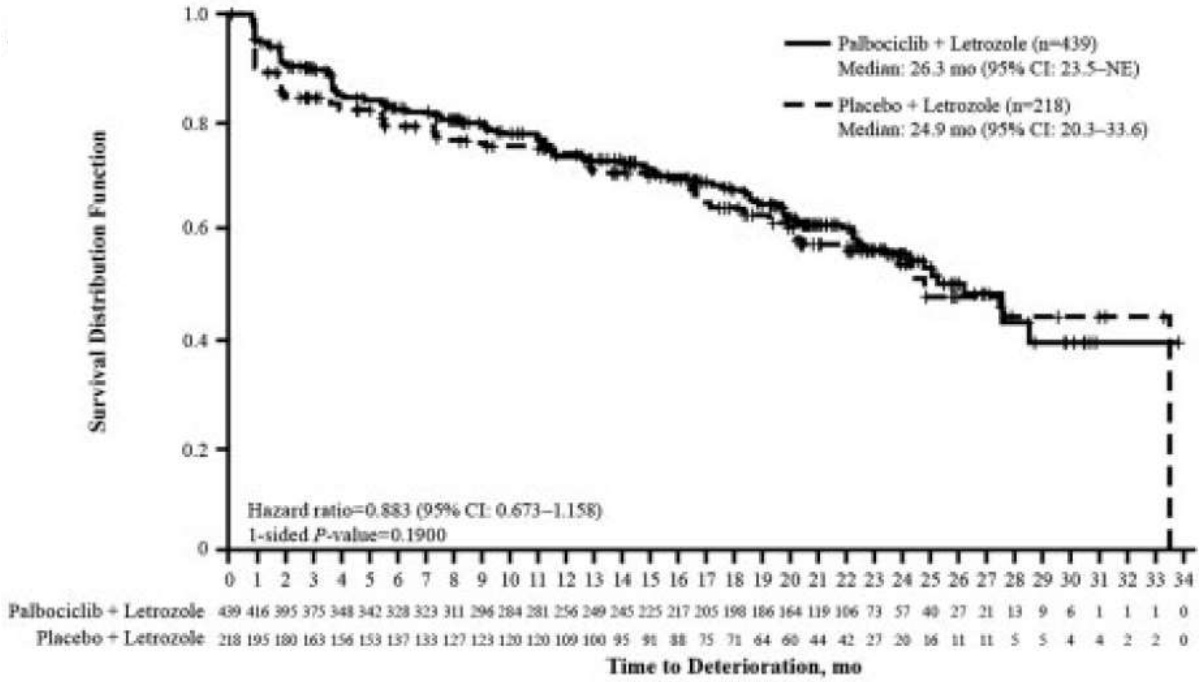
CDK 4/6 inhibitors: toxicity

	Palbociclib	Ribociclib	Abemaciclib
Neutropenia	✓✓✓	✓✓✓	✓✓
Anemia	✓✓	✓✓	✓✓
Thrombocytopenia	✓		
Fatigue	✓	✓	✓
Diarrhea	✓	✓	✓✓
Nausea			✓
QTc prolongation		✓	

Venous thromboembolic events 4.9% **abemaciclib** arm vs 0.6% placebo arm (MONARCH-3)

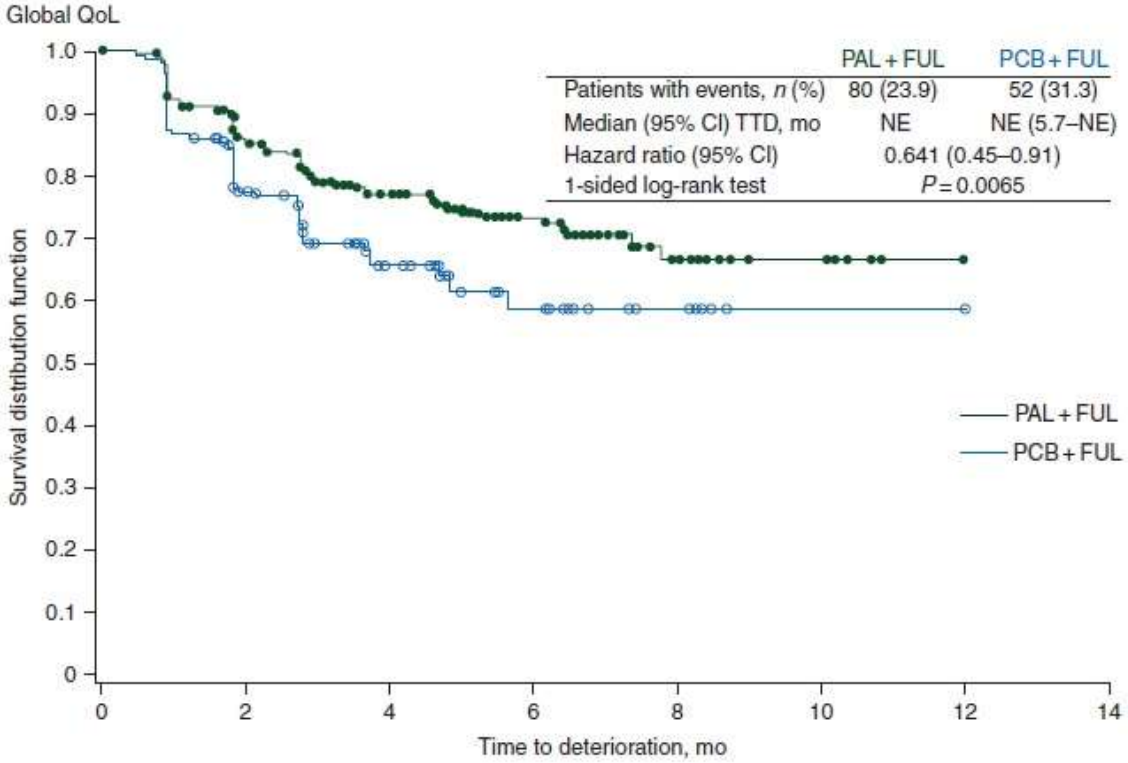
CDK 4/6 inhibitors: QoL

PALOMA-2



Rugo HS, Ann Oncol 2018

PALOMA-3



Harbeck N et al, Ann Oncol 2016

CDK 4/6 inhibitors: regulatory indications

Drug	Dose	Schedule	EMA approval	EMA approval	AIFA
Palbociclib	125 mg daily	3 weeks on/1 week off	**First line, AI-sensitive** with AI **Progressing after ET**, with Fulvestrant	**2016**	**Approval and reimbursement**
Ribociclib	600 mg daily	3 weeks on/1 week off	**First line, AI-sensitive** with AI	**2017**	**Approval and reimbursement**
Abemaciclib	150 mg or 200 mg daily	Continuous	**First line, AI-sensitive** with AI **Progressing after ET** with Fulvestrant **Monotherapy after progression** on ET and CT	**2018** (not in monotherapy)	Approval pending

CDK4/6 POST 1ST LINE FULVESTRANT IS NOT ALLOWED

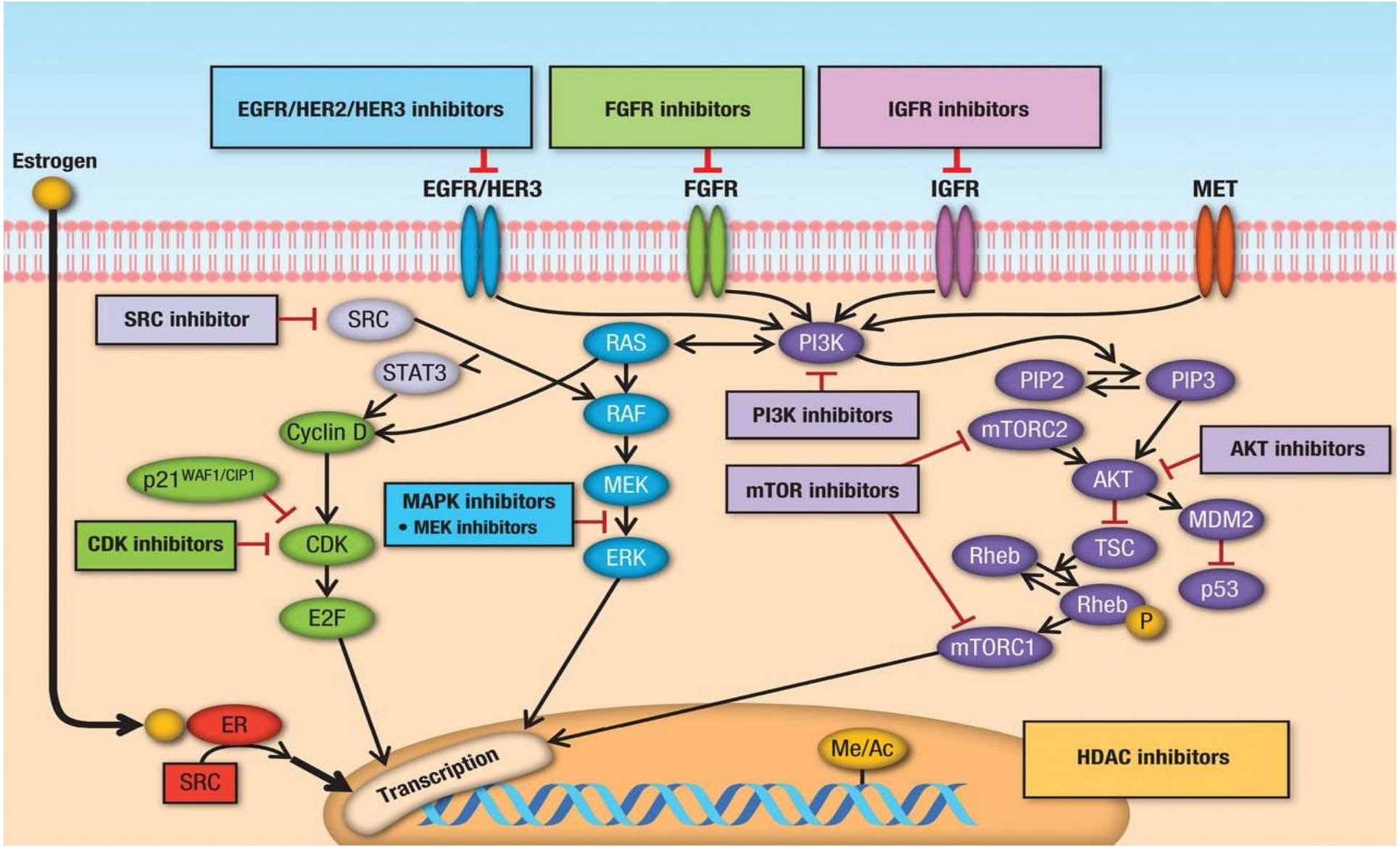
PREDICTIVE BIOMARKERS

- pRb ✗
- P16 ✗
- Ki67 ✗
- ER ✗
- ESR1 gene expression ✗
- CDKN2A gene expression ✗
- CCND1 gene expression ✗
- CCNE1 gene expression ✓

- PIK3CA mut ✗
- TP53 mut ✗
- CDH1 mut ✗
- FGFR1 mut ✗
- RTK mut ✗
- ESR1 mut ✗

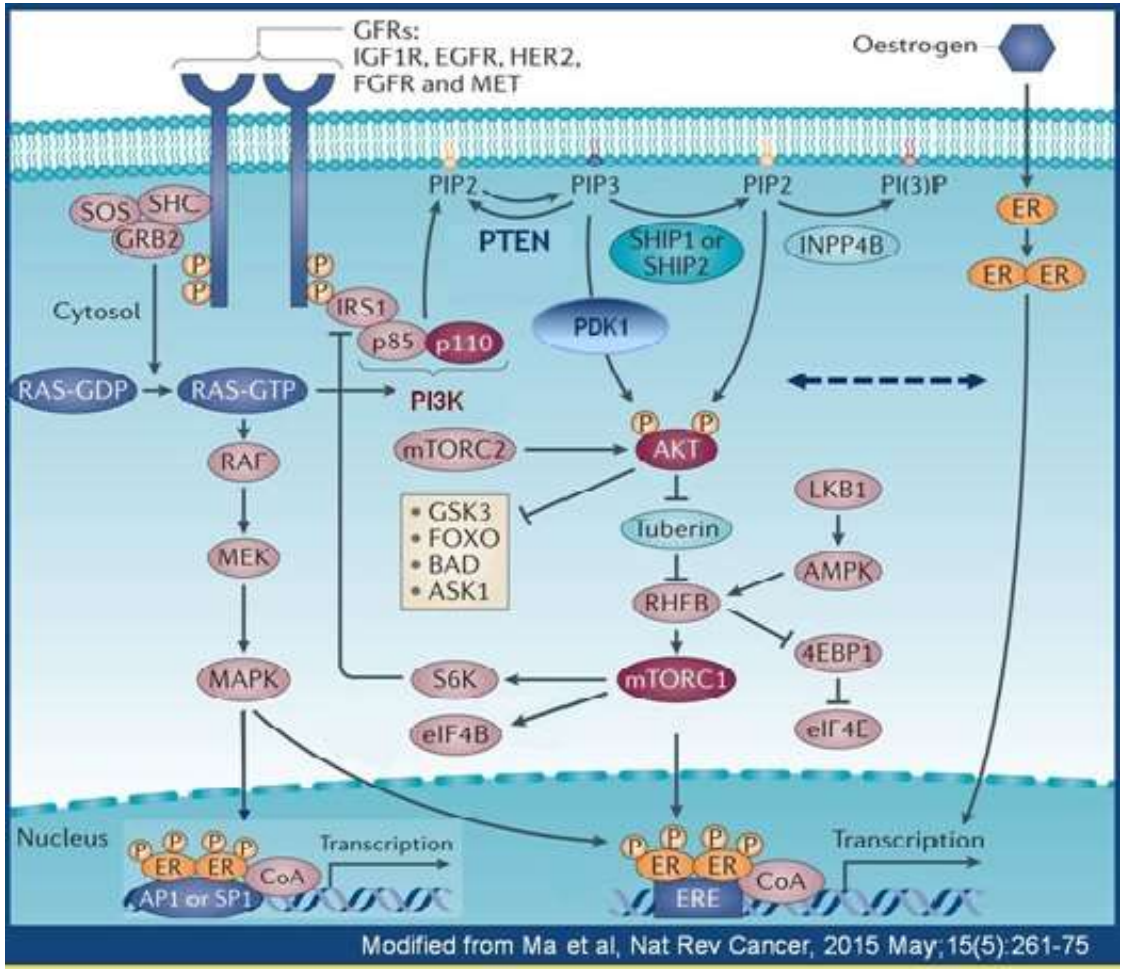
André F, AACR 2017; Hortobagyi G, SABCS 2018; Cristofanilli M, Lancet Oncol 2016; Finn RS, ESMO 2016; Arnedos M, AACR 2016, Fribbens C, JCO 2016; Turner N, AACR 2018

Mechanisms of endocrine resistance



Johnston s et al, J Natl Cancer Inst 2015

PI3K/AKT/mTOR pathway

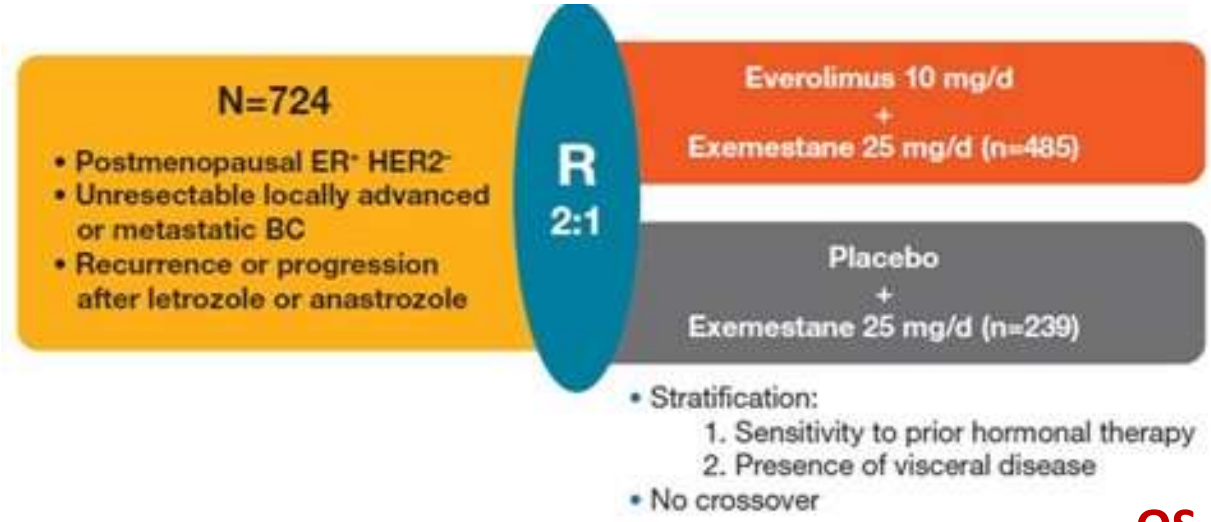


Inhibitor	Drug	Target	Study
Pan-class I PI3K inhibitors	Buparlisib (BKM120)	Pan-PI3K	BELLE-2 BELLE-3
	Pictilisib (GDC-0941)	Pan-PI3K	FERGI
Isoform-specific PI3K inhibitors	Taselisib	p110α	SANDPIPER
	Alpelisib	p110α	SOLAR-1
mTOR inhibitors	Temsirolimus	mTOR	HORIZON
	Everolimus	mTOR	TAMRAD, BOLERO
AKT inhibitor	Ipatasertib	AKT 1/2	Ipatunity

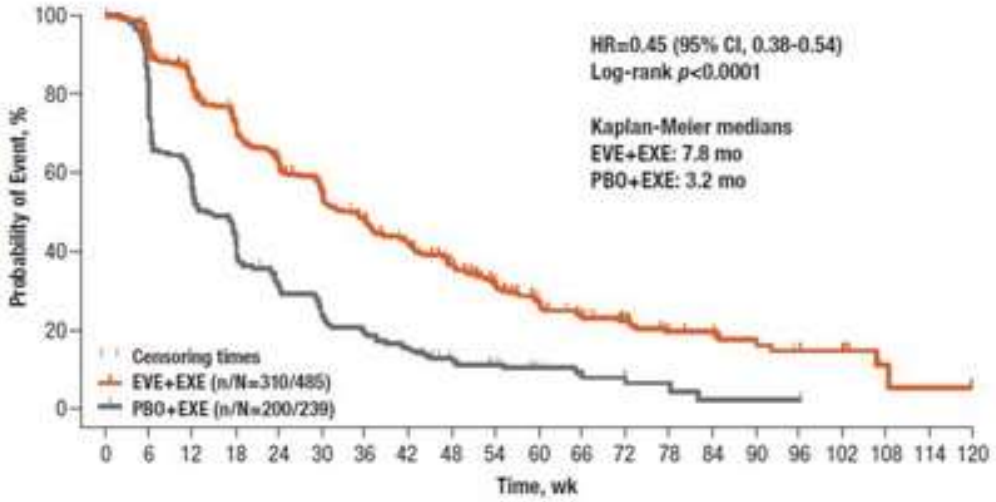
LUMINAL BC: *PIK3CA* mut 30-40%, *AKT1* mut 4%, *PTEN* mut 4%.
Significant cross-talk with ER.

mTOR inhibitors: Everolimus

BOLERO-2

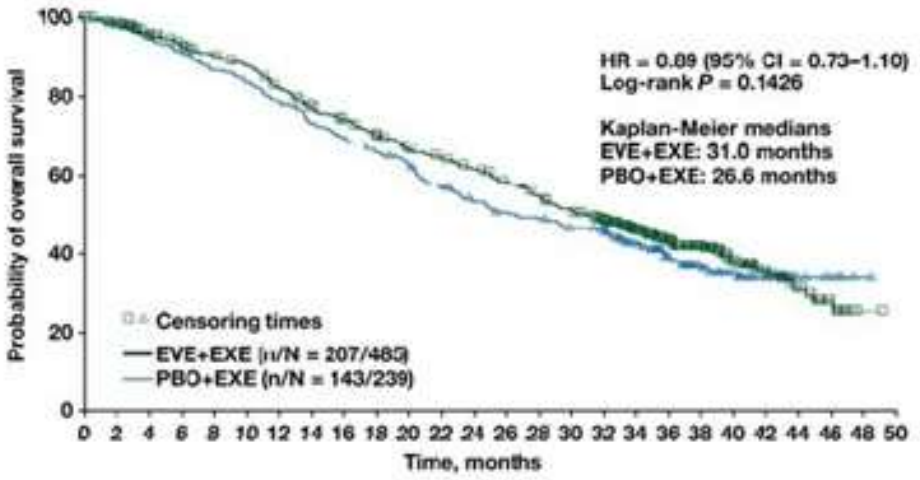


PFS



Yardley DA, Adv Ther, 2013

OS



Piccart , Ann Oncol 2014

mTOR inhibitors: Everolimus

Toxicities

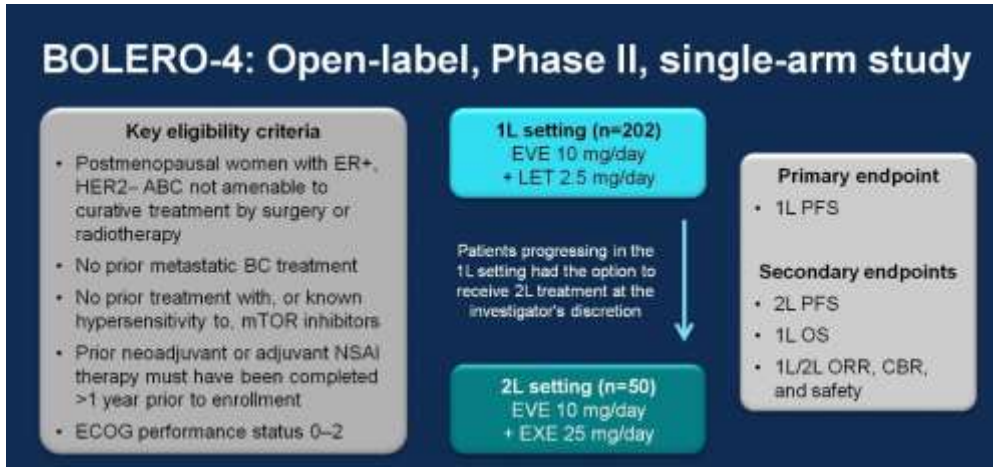
	EVE+EXE (n=482), %					PBO+EXE (n=238), %				
	Grade					Grade				
AE (preferred term)	All	1	2	3	4	All	1	2	3	4
Any AE	100	7	40	44	9	91	26	36	23	5
Stomatitis	59	29	22	8	0	12	9	2	<1	0
Rash	39	29	9	1	0	7	5	2	0	0
Fatigue	37	18	14	4	<1	27	16	10	1	0
Diarrhea	34	26	6	2	<1	19	14	4	<1	0
Nausea	31	21	9	<1	<1	29	21	7	1	0
Decreased appetite	31	19	10	1	0	13	8	4	1	0
Weight decreased	28	10	16	2	0	7	3	5	0	0
Cough	26	21	4	1	0	12	8	3	0	0
Pneumonitis*	16	7	6	3	0	0	0	0	0	0
Hyperglycemia*	14	4	5	5	<1	2	1	1	<1	0

*Incidence <25%, but AE of special interest.
Abbreviations: AE, adverse event; EVE, everolimus; EXE, exemestane; PBO, placebo.

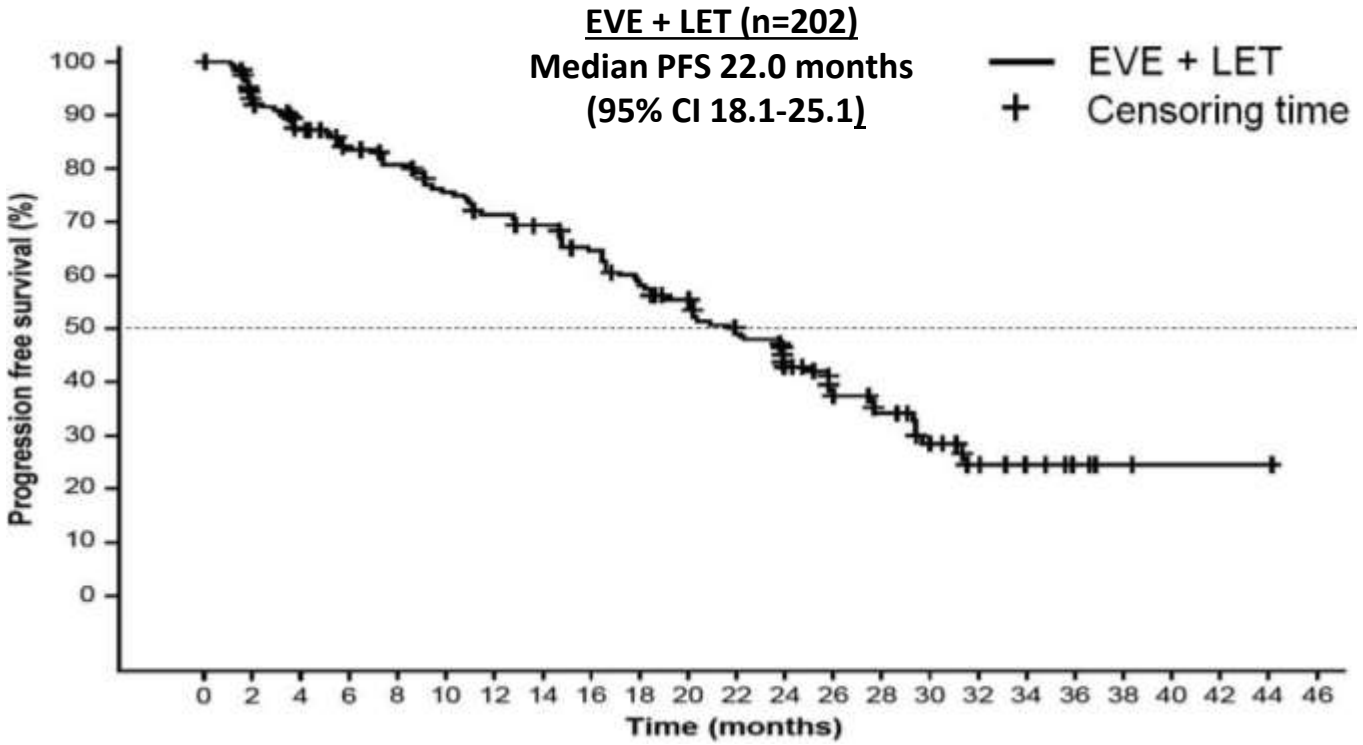
Piccart , ASCO 2012

mTOR inhibitors: first line

Combination of mTor inhibitors and AI in first-line: able to prevent endocrine resistance?

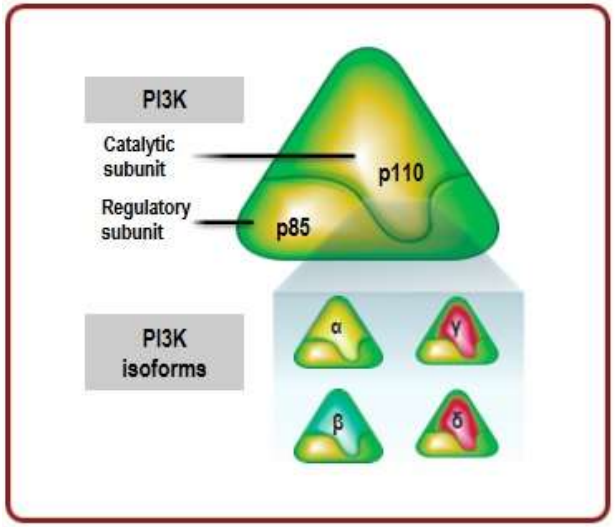


56% no prior Endocrine Rx

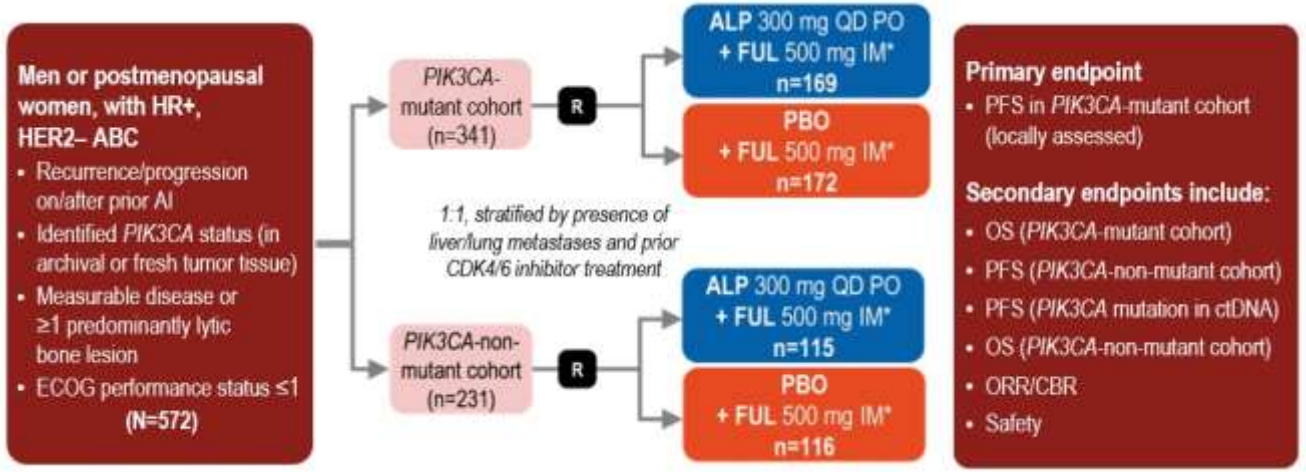


Royce M, JAMA 2018

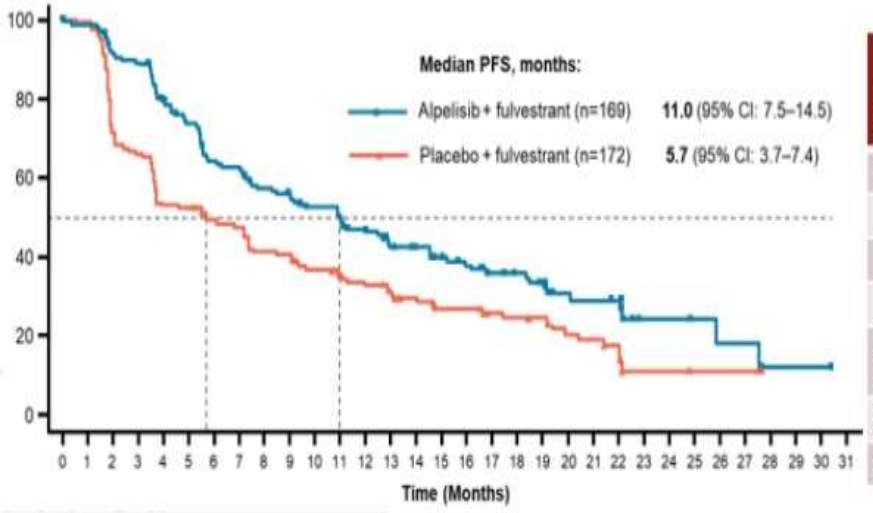
Isoform-specific PI3K inhibitors: Alpelisib



SOLAR-1 study design

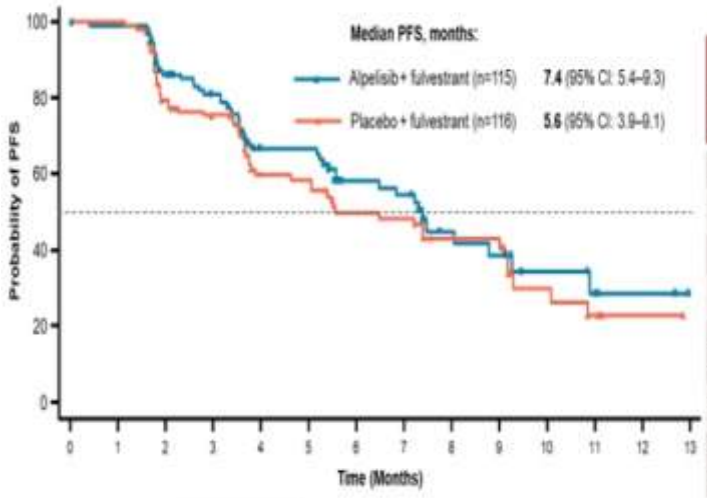


PFS in PIK3CA-mut



Data cut-off: Jun 12, 2018	Alpelisib + fulvestrant (N=169)	Placebo + fulvestrant (N=172)
Number of PFS events, n (%)	103 (60.9)	129 (75.0)
Progression	99 (58.6)	120 (69.8)
Death	4 (2.4)	9 (5.2)
Censored	66 (39.1)	43 (25.0)
Median PFS (95% CI)	11.0 (7.5–14.5)	5.7 (3.7–7.4)
HR (95% CI)	0.65 (0.50–0.85)	
p-value	0.00065	

PFS in PIK3CA-non-mut



Data cut-off: Dec 23, 2016	Alpelisib + fulvestrant (N=115)	Placebo + fulvestrant (N=116)
Number of PFS events, n (%)	49 (42.6)	57 (49.1)
Progression	47 (40.9)	57 (49.1)
Death	2 (1.7)	0
Censored	66 (57.4)	59 (50.9)
Median PFS (95% CI)	7.4 (5.4–9.3)	5.6 (3.9–9.1)
HR (95% CI)	0.85 (0.58–1.25)	
Posterior probability HR<1, %	79.4	

Andrè F, ESMO 2018

Isoform-specific PI3K inhibitors: Alpelisib

Adverse events in total population

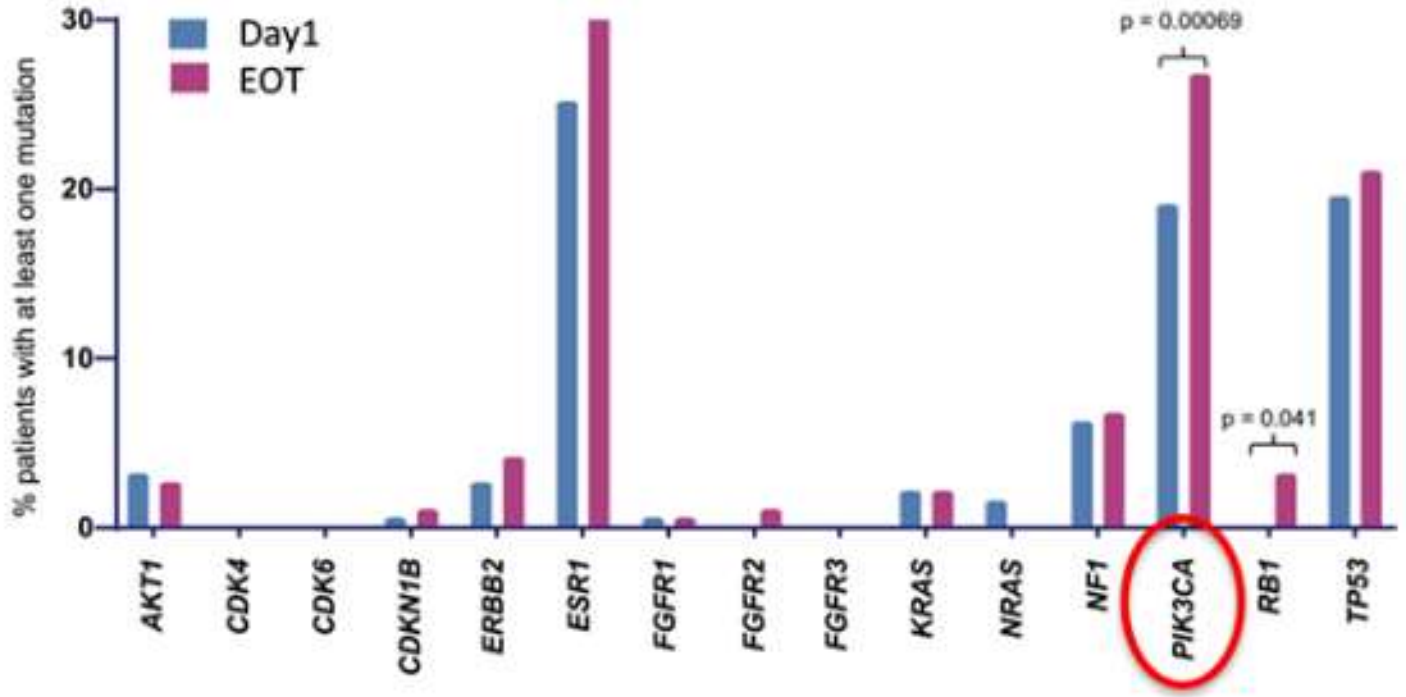
AEs ≥20% in either arm, %	Alpelisib + fulvestrant N=284			Placebo + fulvestrant N=287		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Any adverse event	282 (99.3)	183 (64.4)	33 (11.6)	264 (92.0)	87 (30.3)	15 (5.2)
Hyperglycemia	181 (63.7)	93 (32.7)	11 (3.9)	28 (9.8)	1 (0.3)	1 (0.3)
Diarrhea	164 (57.7)	19 (6.7)	0	45 (15.7)	1 (0.3)	0
Nausea	127 (44.7)	7 (2.5)	0	64 (22.3)	1 (0.3)	0
Decreased appetite	101 (35.6)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash*	101 (35.6)	28 (9.9)	0	17 (5.9)	1 (0.3)	0
Vomiting	77 (27.1)	2 (0.7)	0	28 (9.8)	1 (0.3)	0
Decreased weight	76 (26.8)	11 (3.9)	0	6 (2.1)	0	0
Stomatitis	70 (24.6)	7 (2.5)	0	18 (6.3)	0	0
Fatigue	69 (24.3)	10 (3.5)	0	49 (17.1)	3 (1.0)	0
Asthenia	58 (20.4)	5 (1.8)	0	37 (12.9)	0	0

Dose discontinuation due to AEs: 25% in the alpelisib + fulvestrant and 5% in the placebo + fulvestrant

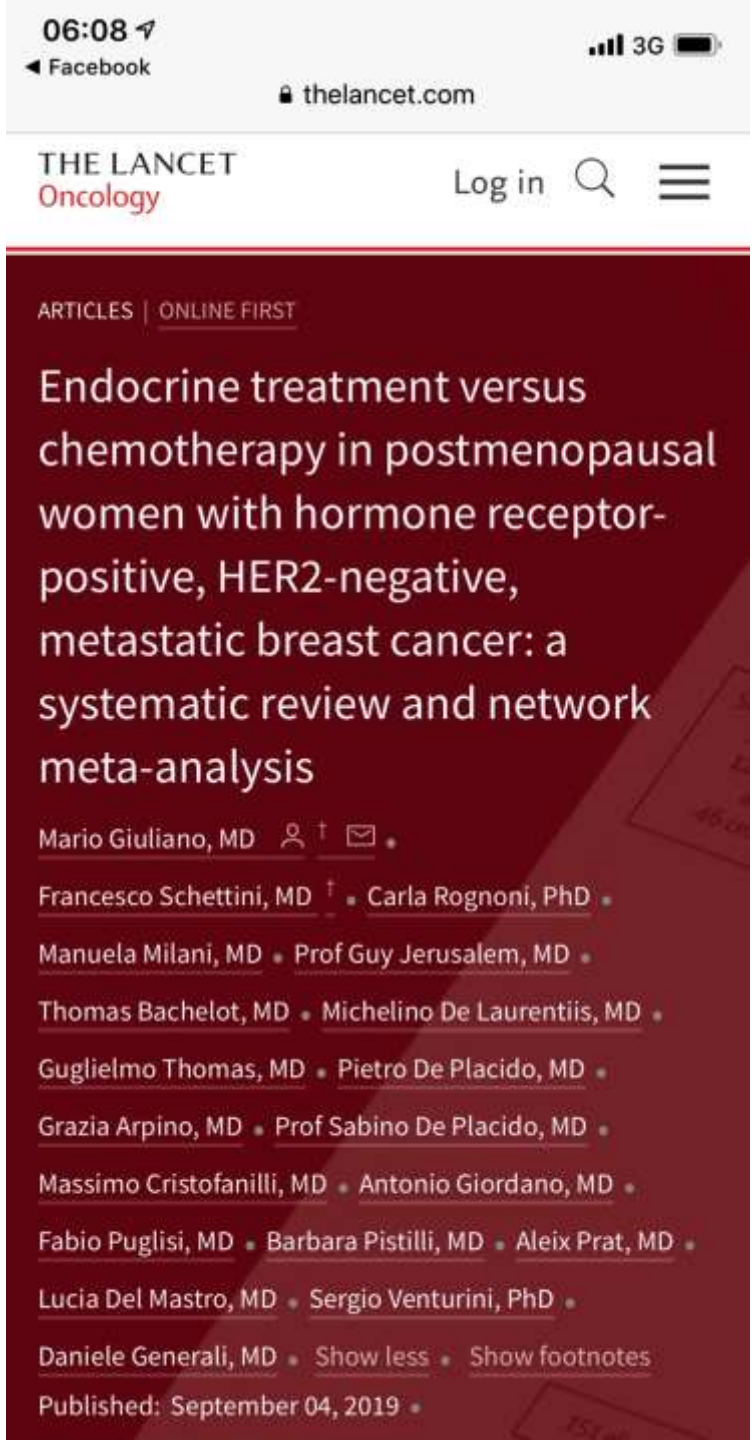
André F, ESMO 2018

Open issues: when to use Pi3k inhibitors?

Identification of PIK3CA-mutant clones after resistance to CDK 4/6 inhibitors



O'Leary, Cancer Discov 2018



The systematic review included all phase II and III randomized controlled trials investigating chemotherapy with or without targeted therapies and hormone therapies with or without targeted therapies as first-line or second-line treatments, or both, in postmenopausal women with HR-positive, HER2-negative metastatic breast cancer published between January 2000 and December 2017; additional recently published relevant randomized controlled trials were also subsequently added. Progression-free survival was the primary outcome measure. All treatments were compared with anastrozole (the most common comparator in trials included in the meta-analysis) and with palbociclib plus letrozole (since it was the first combination of a CDK4/6 inhibitor plus hormone therapy approved for clinical practice and remains a first-line standard of care along with other CDK4/6 inhibitor plus hormone therapy combinations).

A total of 140 studies comprising 50,029 patients were included in the analysis.

Key Findings

Compared with anastrozole alone, progression-

The ASCO Post

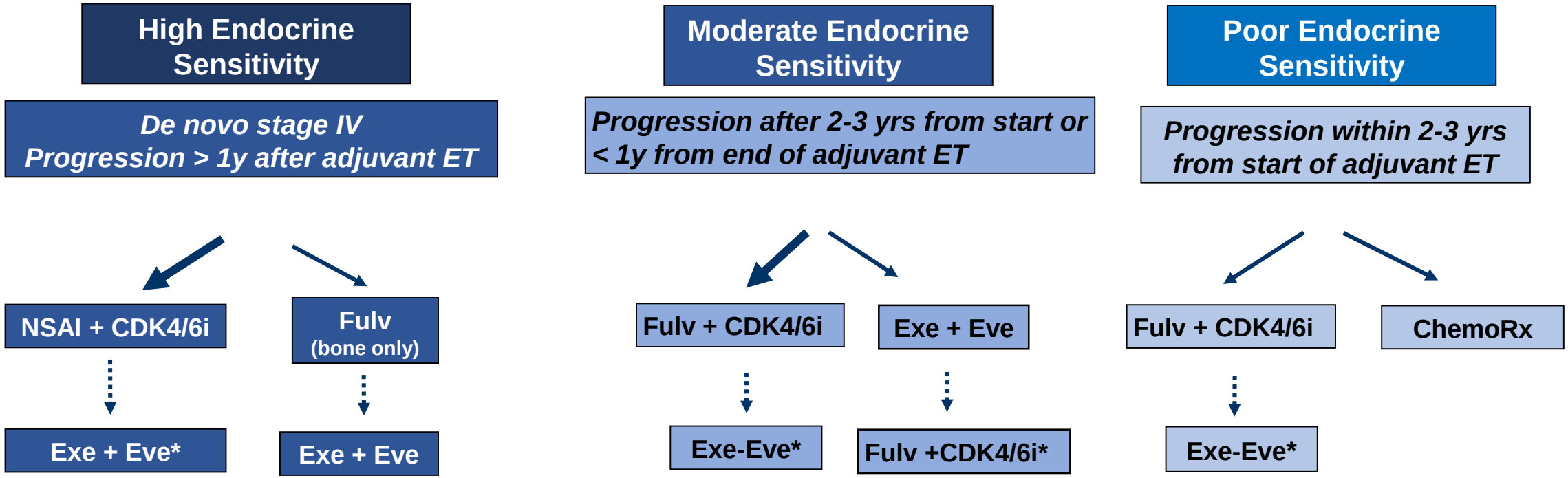
0.42, 95% CrI = 0.28–0.67) and, in patients with *PIK3CA*-mutated disease, alpelisib plus fulvestrant (HR = 0.39, 95% CrI = 0.22–0.66).

> "In the first-line or second-line setting, CDK4/6 inhibitors plus hormone therapies are better than standard hormone therapies in terms of progression-free survival. Moreover, no chemotherapy regimen with or without targeted therapy is significantly better than CDK4/6 inhibitors plus hormone therapies in terms of progression-free survival."
>
> — *Giuliano et al*
>
> *Tweet this quote*

Compared with anastrozole alone, progression-free survival was improved with several regimens of chemotherapy with or without targeted therapies (including anthracycline- and taxane-containing regimens), including fluorouracil plus

189
SHARES

Endocrine Therapy for HR+ MBC: new algorithms



*** Sequences not supported by data from clinical trials**

PIK3CA (and ESR1) mutational status on ctDNA might have a role in treatment sequencing