Ospedale Classificato Equiparato
Sacro Cuore - Don Calabria
Presidio Ospedaliero Accreditato - Regione Veneto

Sacro Cuore Don Calabria
Cancer Care Center
Negrar - Verona

Incontri di aggiornamento del Dipartimento Oncologico

Il carcinoma mammario metastatico HR+/HER2- negativo: i nuovi algoritmi alla luce delle nuove opzioni terapeutiche

Responsabile Scientifico:
DOTT.SSA STEFANIA GORI

Lunedì 16 aprile 2018

SEDE: *"Centro Formazione e Solidarietà"*
Ospedale "Sacro Cuore - Don Calabria"
Via Don Angelo Sempreboni, 5 - 37024 Negrar (Verona)

Il sottogruppo metastatico HR+/HER2-: quali trattamenti sistemici nel 2018?

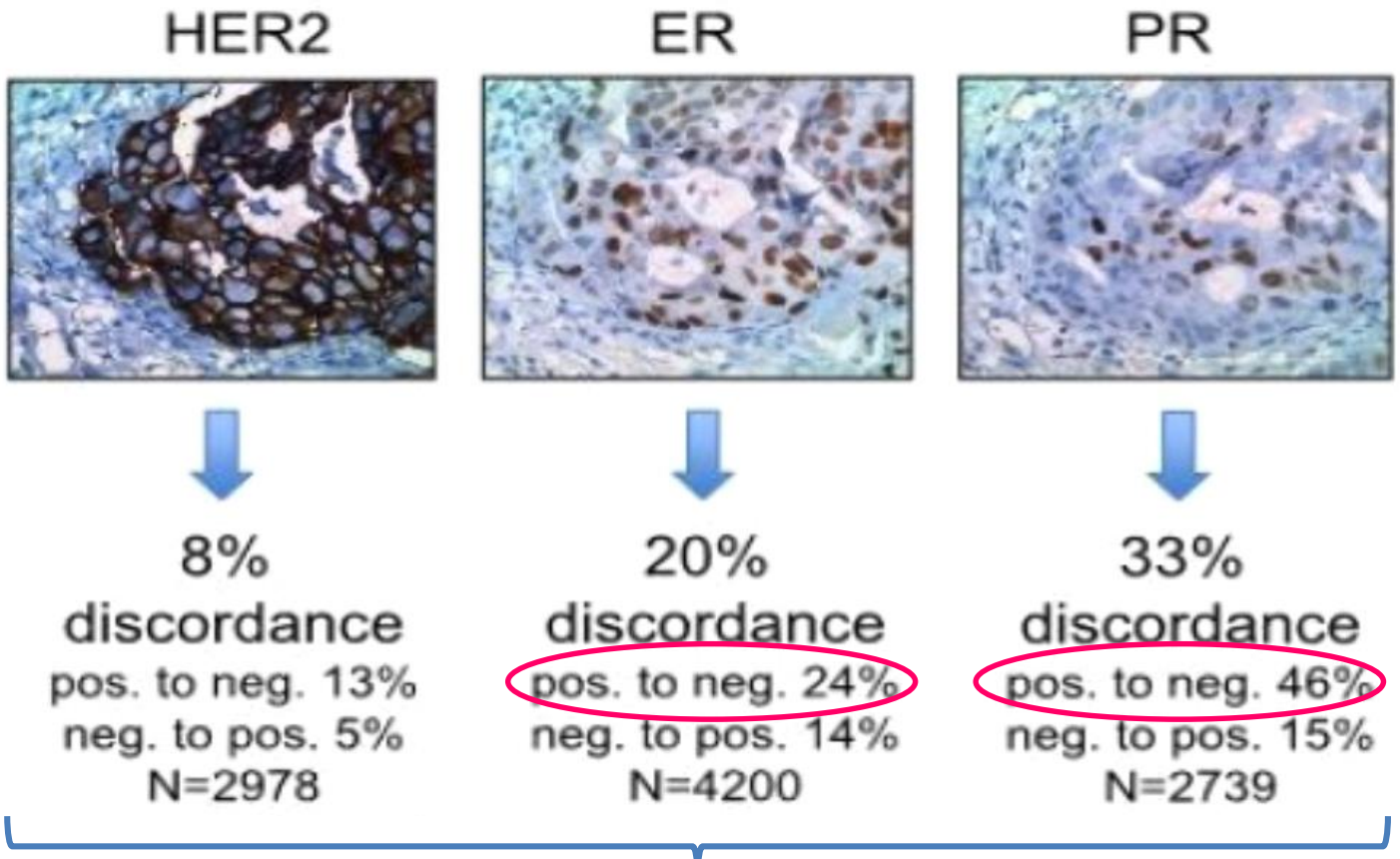
Dr. Monica Turazza

Oncologia Medica - Negrar

«GOOD CLINICAL PRACTICE» IN HR+/HER2- METASTATIC BREAST CANCER

- Treatment choice based on type of adjuvant therapy, disease-free interval, extent of recurrent disease
- Treatment balance between efficacy and toxicity (chronic disease)
- Hormone therapy recommended as initial treatment except in case of imminent life-threatering disease or in rapid visceral recurrence during adjuvant endocrine therapy
- Treatment administered until there is unequivocal evidence of disease progression (documented by imaging, clinical examination, disease-related symptoms)
- Patients should be encoureged to consider enrolling in clinical trials

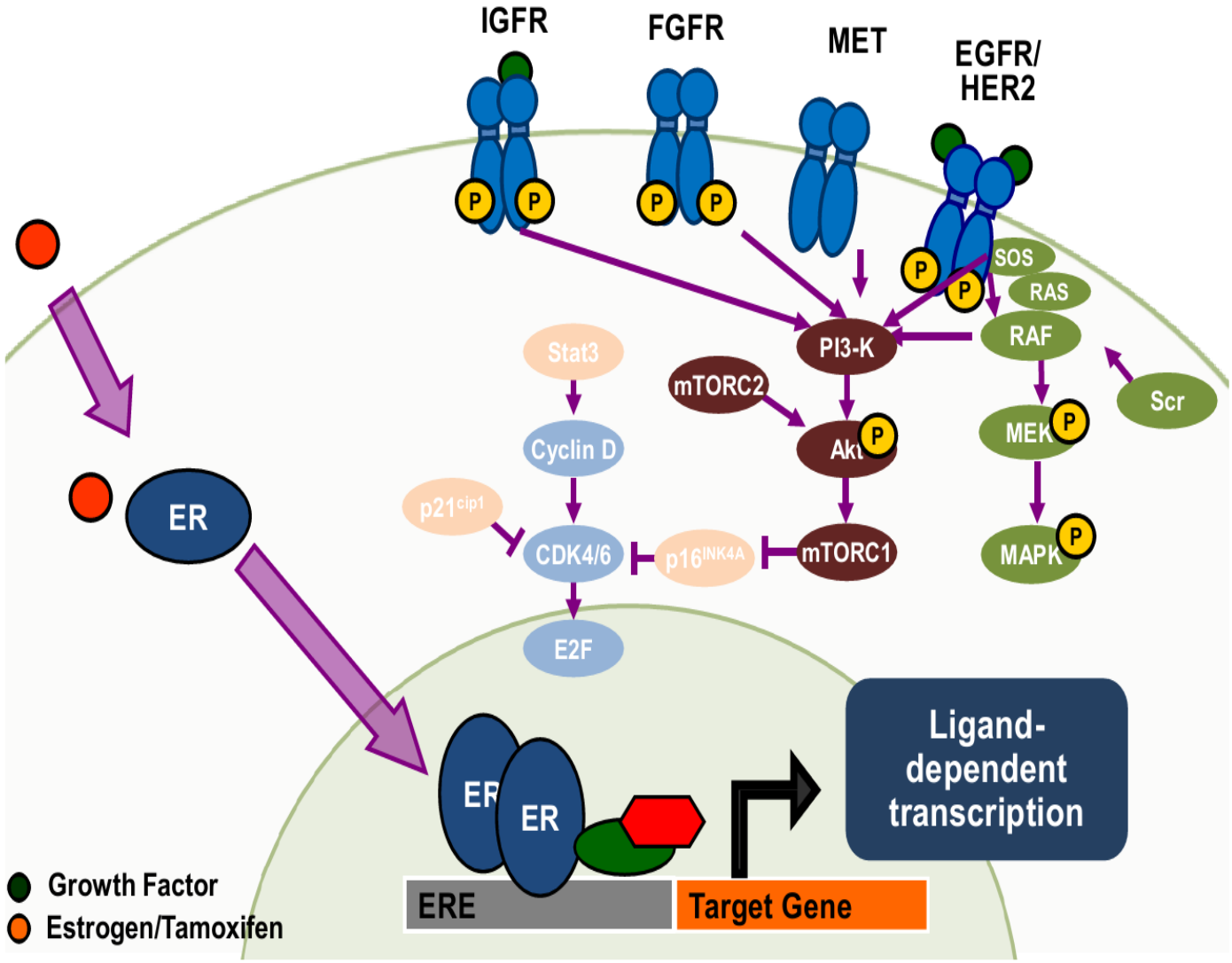
Biomarchers changement between primary and recurrent/metastatic tumor



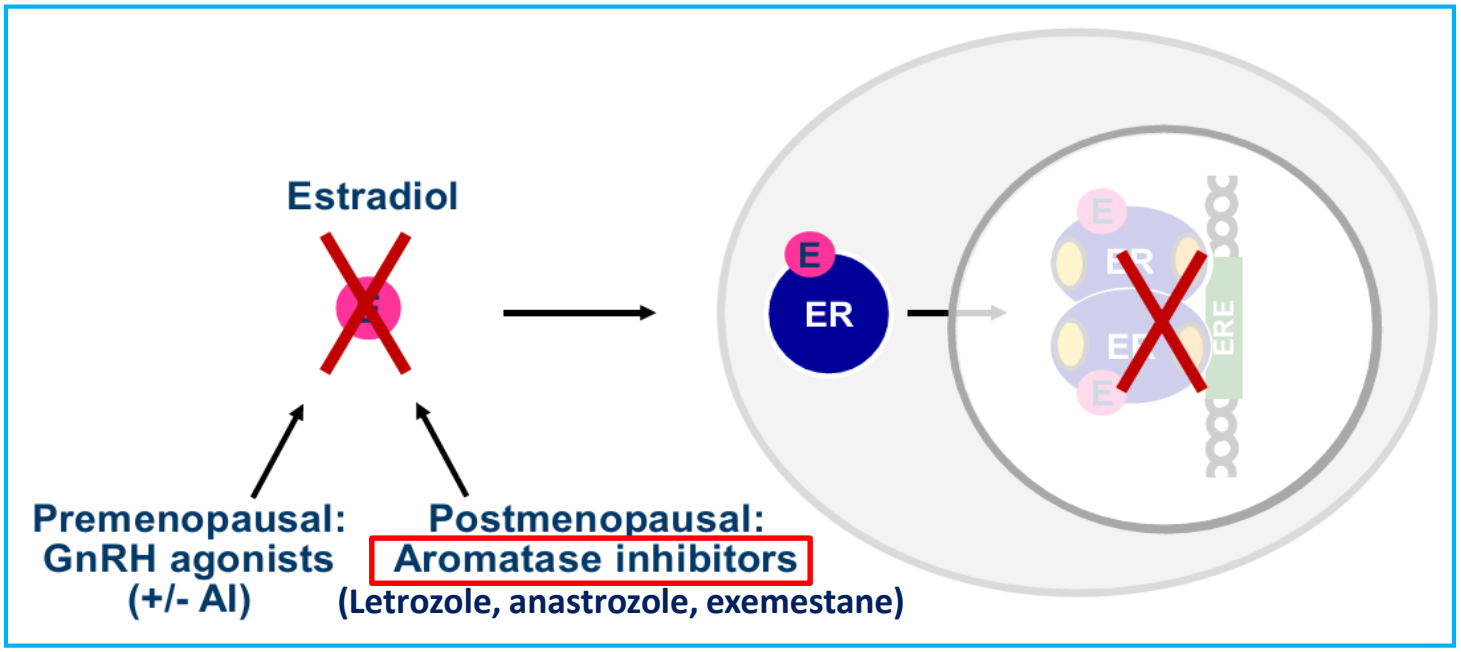
Necessity to re-testing on recurrent/metastatic disease
Discordance caused by analytical variability
Positivity don't indicate funtionality of receptors

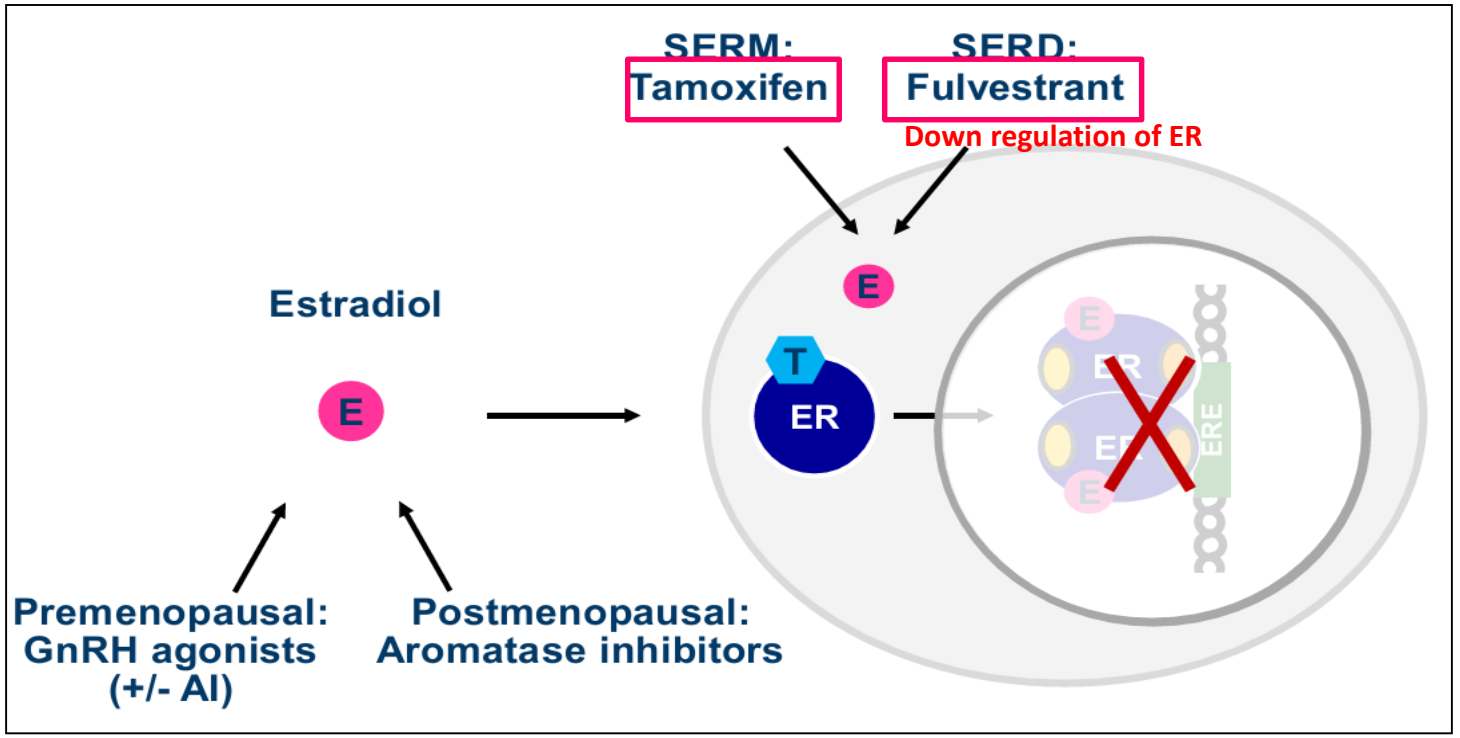
Aurilio et al, EJC 2015

ER-Signaling and Cellular Signaling Network



Adapted from: Johnston S. *Clin Cancer Res*. 2005;11(2 Pt 2):889S-899S.





PRINCIPLES OF ENDOCRINE THERAPY IN BREAST CANCER

Endocrine Trials in First-Line MBC

(Menopausal status)

AI vs Tamoxifen

Trial	Treatment	No. Patients	TTP/PFS, mo	ORR, %	CBR, %
Bonneterre et al[a]	Anastrozole vs tamoxifen	340 328	8.2 8.3	32.9 32.6	56.2 55.5
Nabholtz et al[a]	Anastrozole vs tamoxifen	171 182	11.1 5.6	21.1 17.0	59.1 45.6
Mouridsen et al[a]	Letrozole vs tamoxifen	453 454	9.4 6.0	32 21	50 38
Paridaens et al[a]	Exemestane vs tamoxifen	182 189	9.9 5.8	46 31	NR NR
Chernozemsky et al[a]	Exemestane vs tamoxifen	83 84	12 8.3	37.4 29.8	79.5 78.6

a. Cardoso F e al. Cancer Treat Rev. 2013; 39:457-65

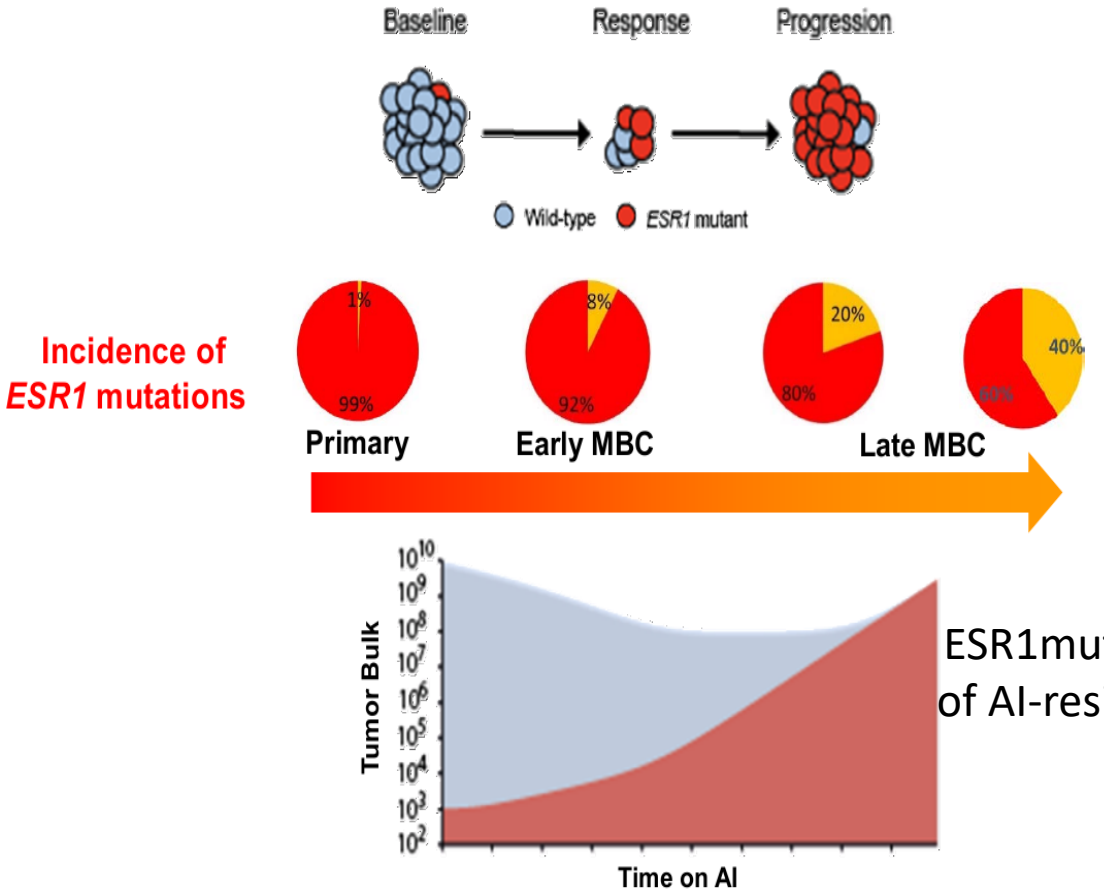
MECHANISMS OF ENDOCRINE RESISTANCE In HR-positive METASTATIC BREAST CANCER

- Activating mutations of ESR1
- Ligand independent ER activation through ER phosphorylation
- Up-regulation of alternative signaling pathways

TARGET THERAPY?

Acquired Somatic Mutations: *ESR1*

***ESR1* mutations are acquired/selected during treatment with aromatase inhibitors**



ESR1mutations occur in 20-40% of AI-resistant ER+ breast cancer

Zhang QX, et al. *Clin Cancer Res.* 1997;3(12 Pt 1):2329-2335. Li S, et al. *Cell Rep.* 2013;4(6):1116-1130. Toy W, et al. *Nat Genet.* 2013;45(12):1439-1445. Robinson DR, et al. *Nat Genet.* 2013;45(12):1446-1451. Merenbakh-Lamin K, et al. *Cancer Res.* 2013;73(23):6856-6864. Jeselsohn R, et al. *Clin Cancer Res.* 2014;20(7):1757-1767.

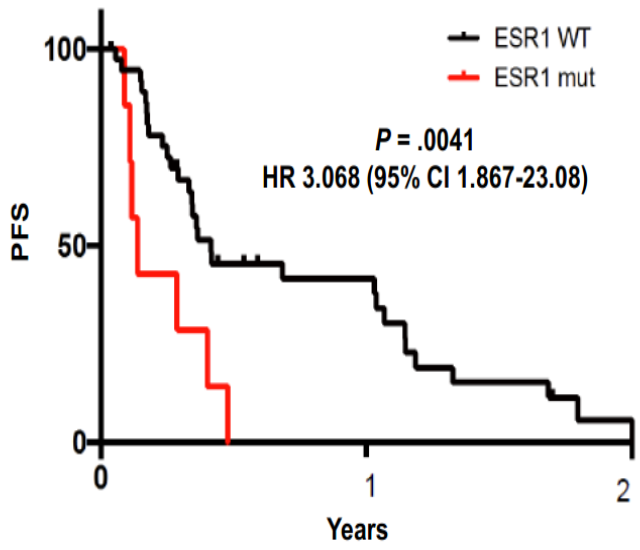
ESR1: gene encoding the ER → ESR1-mutated change the function of ER leading to resistance

ESR1 Mutations Linked With Resistance To Aromatase Inhibitors

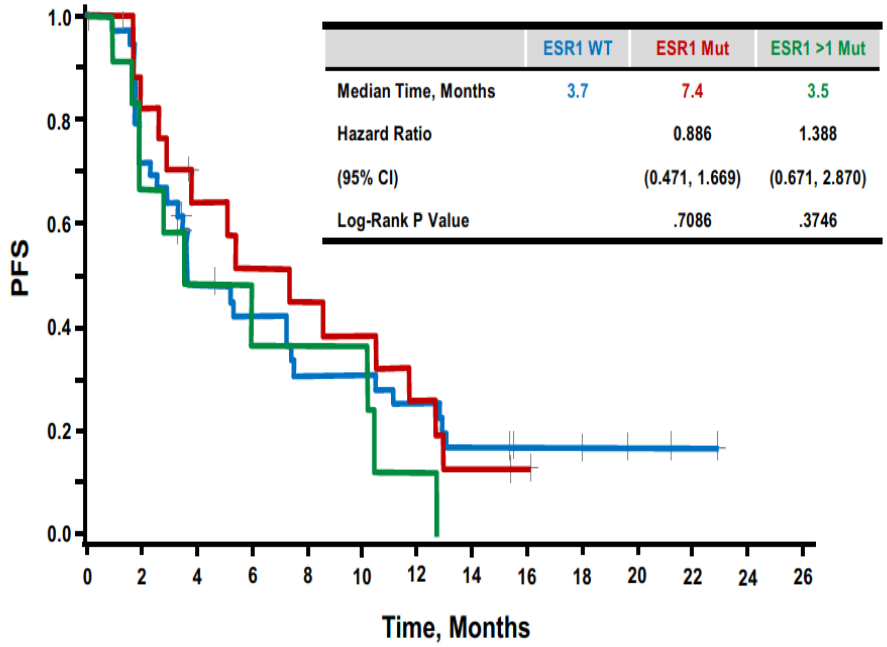
***ESR1* mutations result in constitutively activated ER and endocrine resistance →**

SERD more sensitive than AI or SERM

ESR1 Mutation Predictive of Poor PFS in Patients Treated With AI



ESR1 Mutation not Predictive PFS in Patients Treated With Fulvestrant



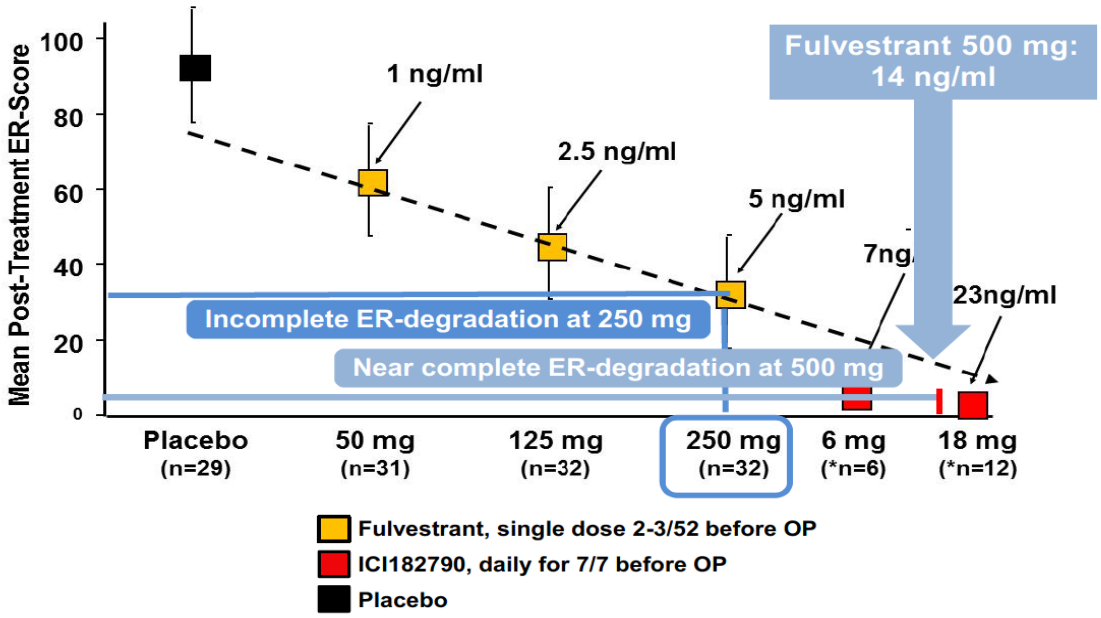
	ESR1 WT	ESR1 Mut	ESR1 >1 Mut
Median Time, Months	3.7	7.4	3.5
Hazard Ratio		0.886	1.388
(95% CI)		(0.471, 1.669)	(0.671, 2.870)
Log-Rank P Value		.7086	.3746

Mut, mutated; SERD, selective estrogen receptor down-regulator ; SERM, selective estrogen receptor modulators; WT, wild type

Schiavon G, et al. *Sci Transl Med.* 2015;7(313):313ra182. Spoerke JM, et al. *Nat Commun.* 2016;7:11579.

Dose Effect of Fulvestrant

Dose effect for fulvestrant with doses >250 mg more effective for ER down-regulation
→ Oral SERDs might allow higher doses for more complete ER degradation



Robertson JF, et al. *Cancer Res.* 2001;61(18):6739-6746. DeFriend DJ, et al. *Cancer Res.* 1994;54(2):408-414.

CONFIRM Phase 3, Double-Blind Trial

Compared dose of fulvestrant 500 mg (n.362) vs 250 mg (n. 374)

- PFS was significant longer for fulvestrant 500 mg: HR=0.80; 95%CI: 0.68, 0.94; p=0.06 or a 20 % reduction for progression
- ORR was similar for fulvestrant 500 mg and 250 mg (9.1% vs 10.2% respectively)
- CBR was 45.6% for fulvestrant 500 mg and 39.6% for fulvestrant 250

Di Leo et al J Clinc Oncol 2010;28: 4594-4600

FALCON trial: anastrozole vs Fulvestrant in HR+/HER- advanced breast cancer

- Randomized, double-blind, multicenter, phase 3 trial
- Postmenopausal women with inoperable locally advanced or metastatic ER-positive/HER2-negative breast cancer (N = 462)
- No prior hormone therapy
- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, DOR, EDOR, CBR, DOCB, EDOCB, HRQoL, safety

Fulvestrant 500 mg IM days 0, 14, 28, then monthly thereafter (n = 230)

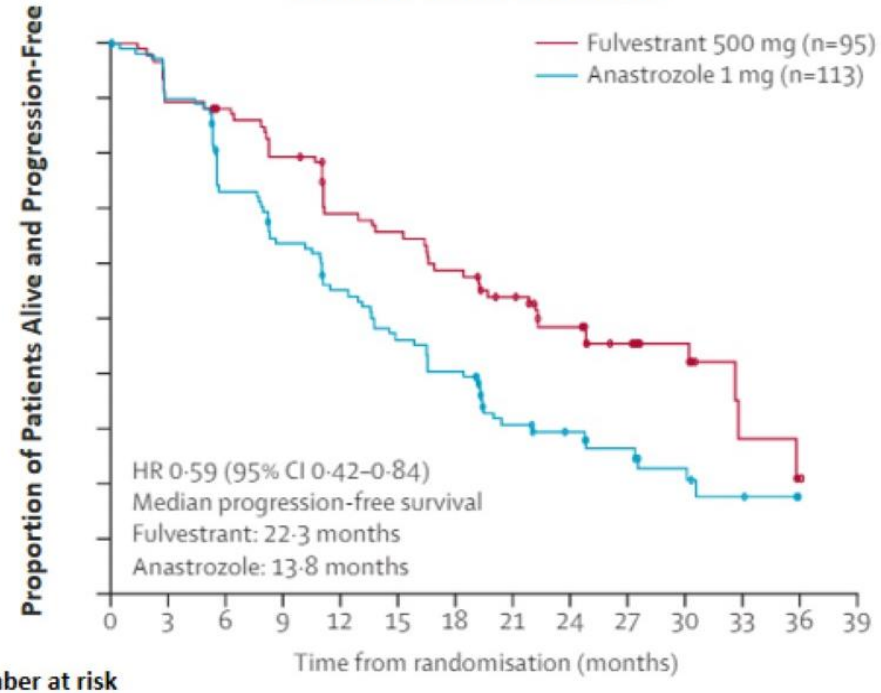
OR

Anastrozole 1 mg every day (n = 232)

Patients allowed 1 line of chemotherapy

Robertson J et al. Lancet 2016;388:2997-3005

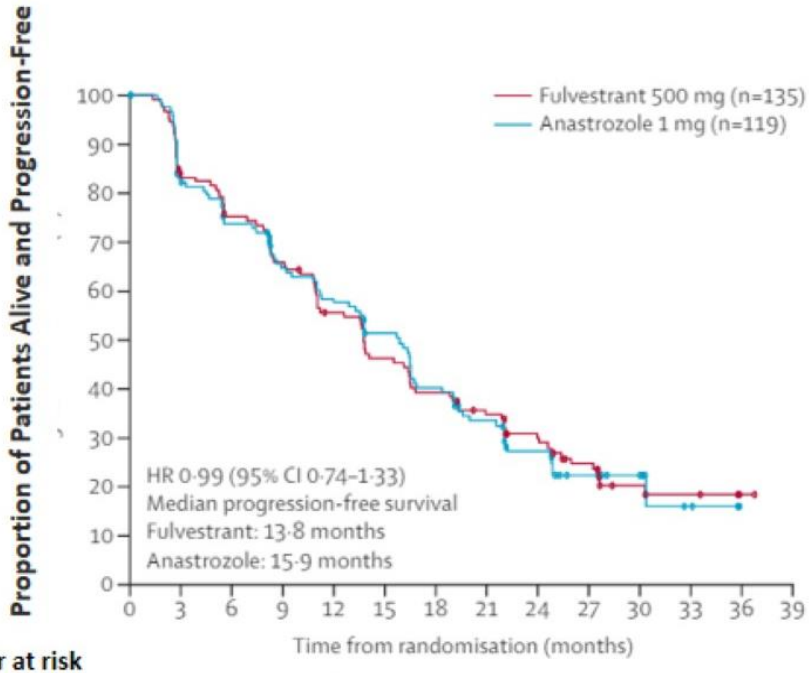
Without Visceral Disease



Number at risk

Fulvestrant	95	84	80	72	60	57	51	44	34	23	14	4	1	0
Anastrozole	113	98	78	67	56	47	41	27	21	16	11	6	0	0

With Visceral Disease

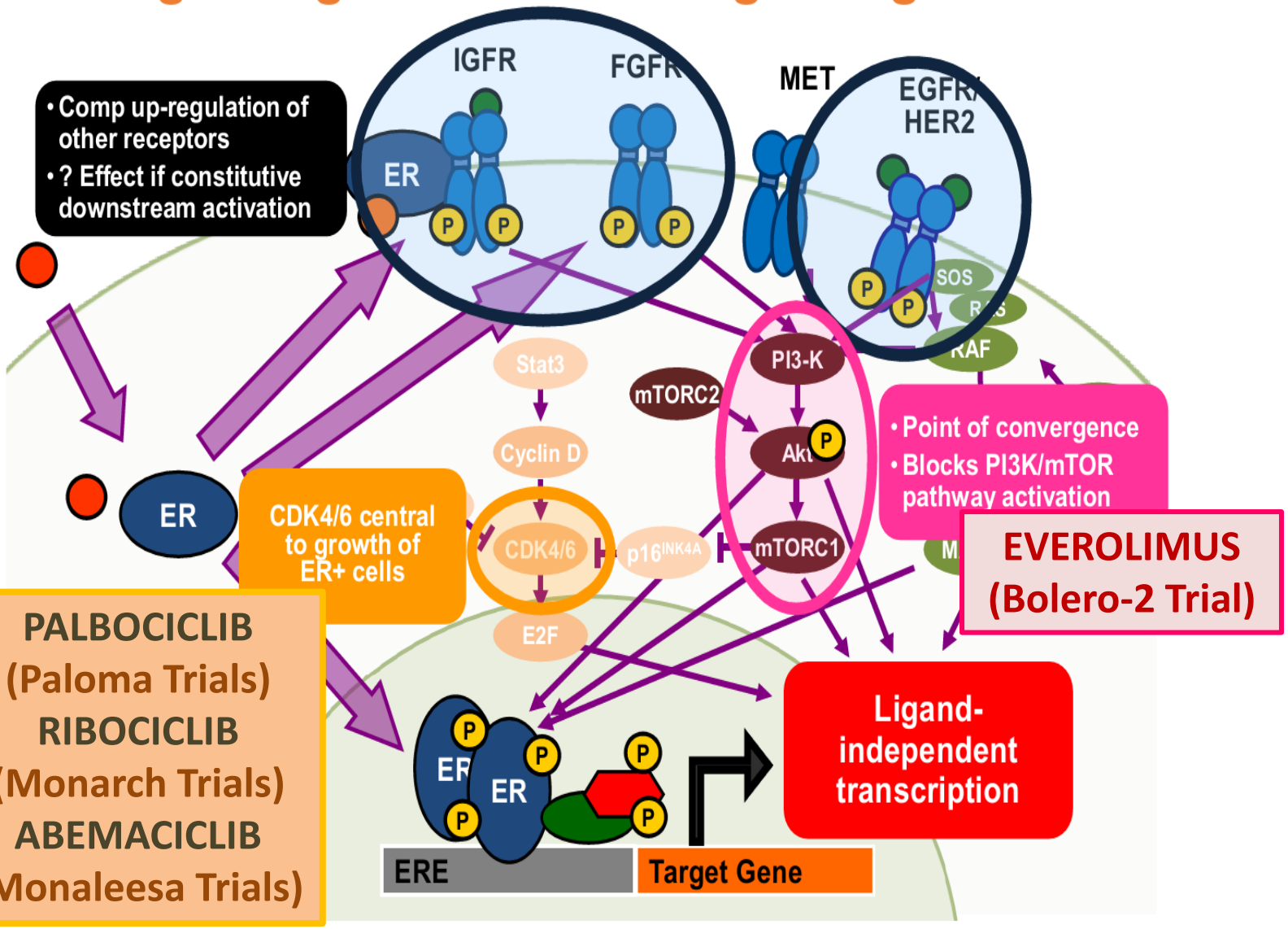


Number at risk

Fulvestrant	135	103	91	78	64	53	45	37	29	21	10	7	1	0
Anastrozole	119	96	84	72	64	55	43	33	24	15	11	4	0	0

Time, mo

ER-Signaling and Cellular Signaling Network



Adapted from: Johnston S. *Clin Cancer Res*. 2005;11(2 Pt 2):889S-899S.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer

José Baselga, M.D., Ph.D., Mario Campone, M.D., Ph.D., Martine Piccart, M.D., Ph.D., Howard A. Burris III, M.D., Hope S. Rugo, M.D., Tarek Sahmoud, M.D., Ph.D., Shinzaburo Noguchi, M.D., Michael Gnant, M.D., Kathleen I. Pritchard, M.D., Fabienne Lebrun, M.D., J. Thaddeus Beck, M.D., Yoshinori Ito, M.D., Denise Yardley, M.D., Ines Deleu, M.D., Alejandra Perez, M.D., Thomas Bachelot, M.D., Ph.D., Luc Vittori, M.Sc., Zhiying Xu, Ph.D., Pabak Mukhopadhyay, Ph.D., David Lebwohl, M.D., and Gabriel N. Hortobagyi, M.D.

N ENGL J MED 366;6 NEJM.ORG FEBRUARY 9, 2012

BOLERO-2: Everolimus + Exemestane vs Placebo + Exemestane

- Randomized (2:1 ratio), double-blind, phase 3 study
- Patients with HR+ advanced breast cancer who had recurrence or progression on prior AI therapy in adjuvant setting (N = 724)
- Stratified according to presence of visceral metastasis and previous sensitivity to endocrine therapy
- Primary endpoint: PFS
- Secondary endpoints: OS, response rate, safety

Everolimus + Exemestane (n = 485)

OR

Placebo + Exemestane (n = 239)

Baselga J, et al. *N Engl J Med.* 2012;366:520-529.

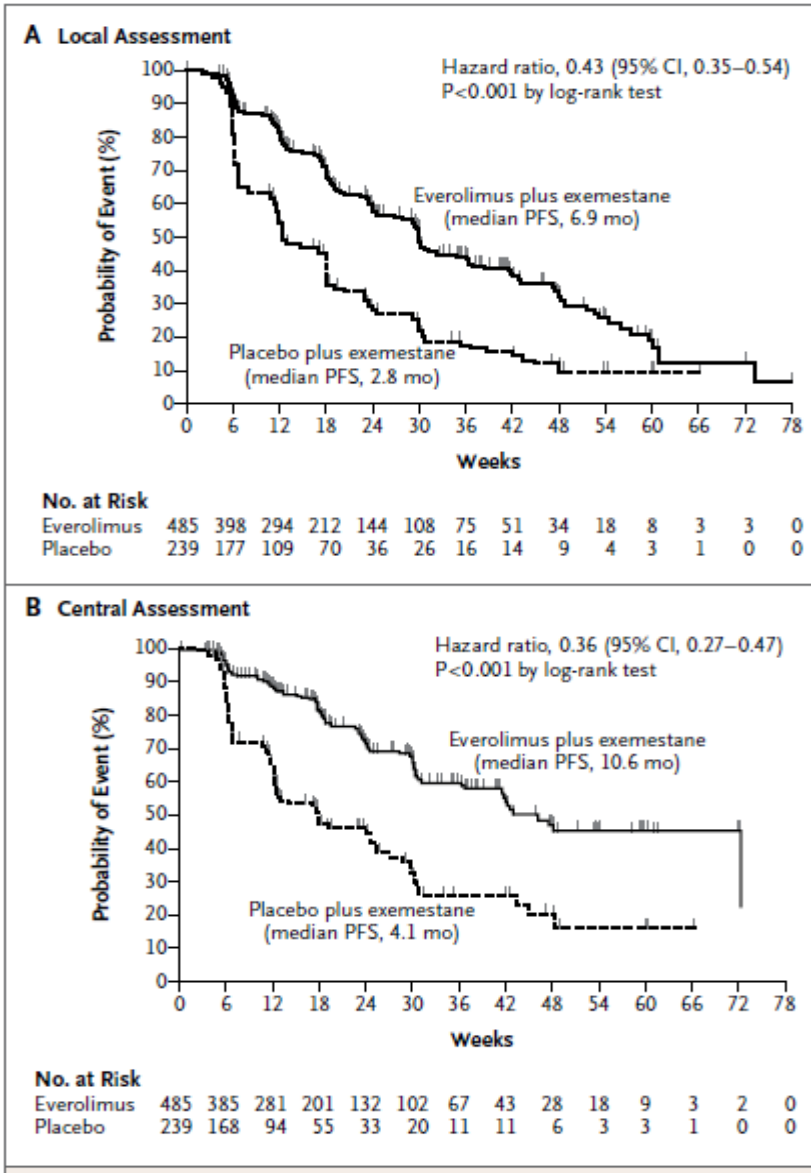


Figure 1. Kaplan–Meier Plot of Progression-free Survival.

Panel A shows progression-free survival on the basis of local assessment of radiographic studies, and Panel B shows central assessment. PFS denotes progression-free survival.

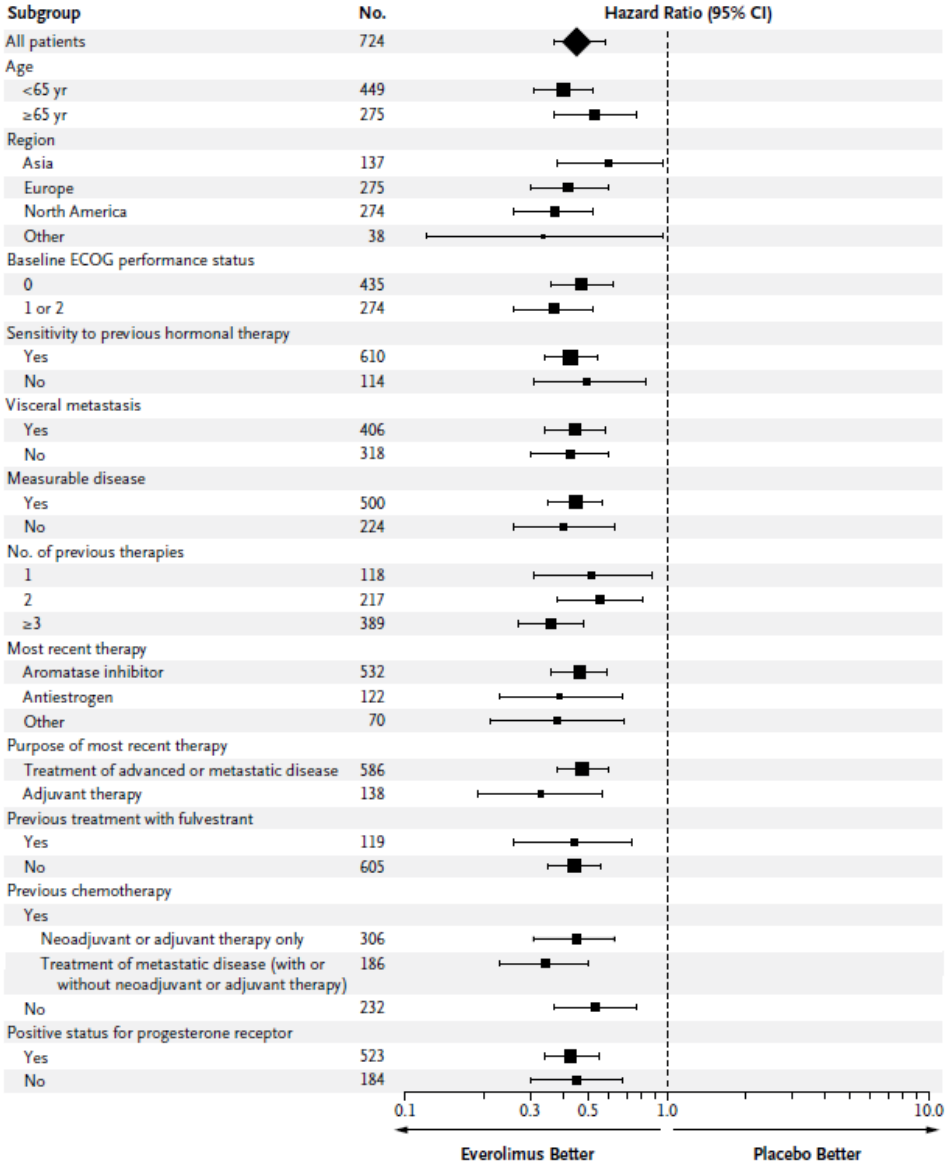


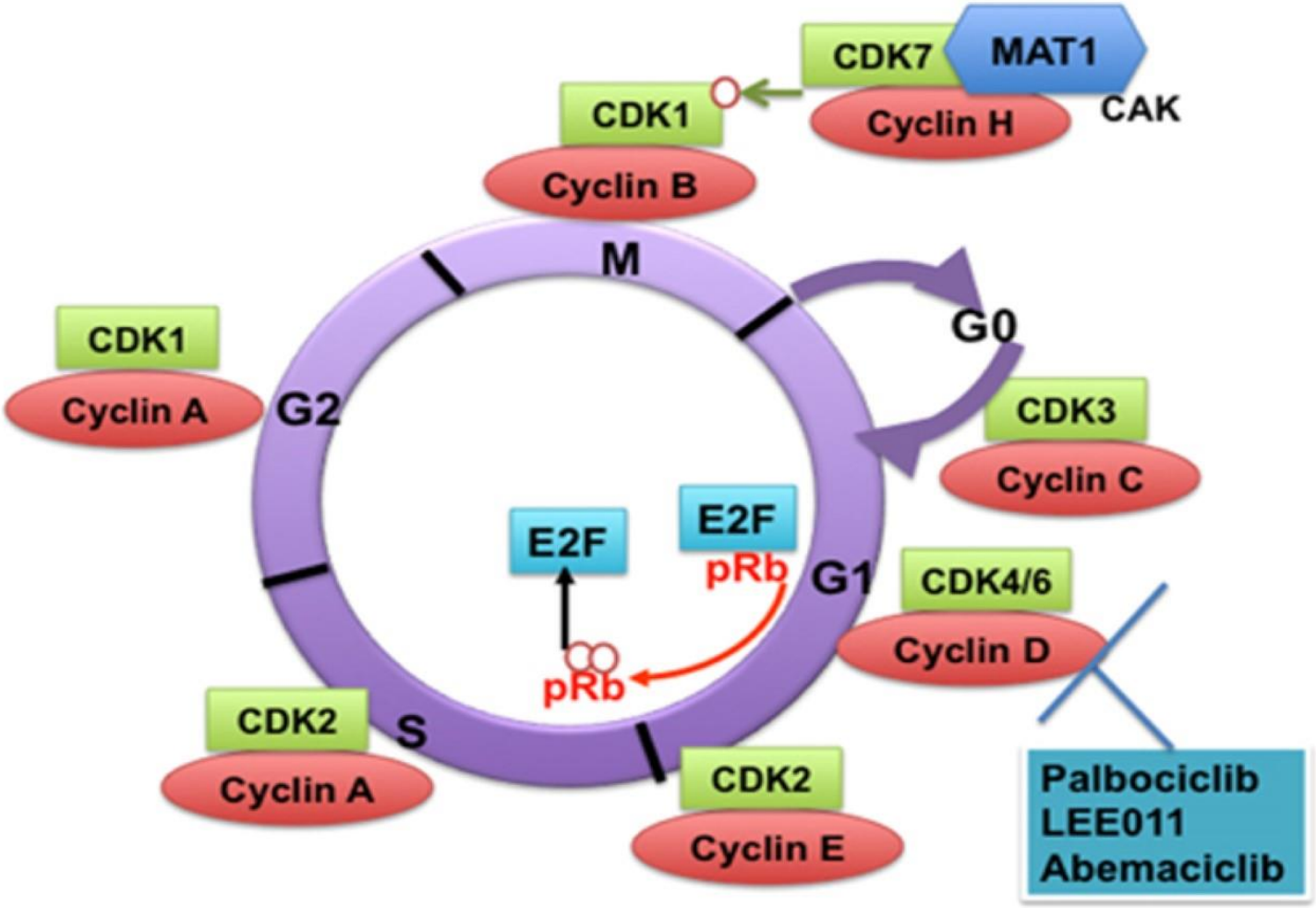
Figure 2. Consistency of Results for Progression-free Survival across the Various Subgroups.

Scores for Eastern Cooperative Oncology Group (ECOG) performance status range from 0 to 5, with 0 indicating that the patient is fully active, 1 indicating that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature, and 2 indicating that the patient is ambulatory and capable of all self-care but unable to work. The number of patients may not add up to 724 owing to missing baseline data. The size of each square is proportional to the number of patients in the subgroup. The data are shown on a semi-logarithmic scale.

Table 2. Adverse Events Irrespective of Relationship to Study Treatment (with at Least 10% Incidence in the Everolimus–Exemestane Group).

Adverse Event	Everolimus and Exemestane (N=482)			Placebo and Exemestane (N=238)		
	Any Event	Grade 3 Event	Grade 4 Event	Any Event	Grade 3 Event	Grade 4 Event
	percent					
Stomatitis	56	8	0	11	1	0
Rash	36	1	0	6	0	0
Fatigue	33	3	<1	26	1	0
Diarrhea	30	2	<1	16	1	0
Decreased appetite	29	1	0	10	0	0
Nausea	27	<1	<1	27	1	0
Cough	22	1	0	11	0	0
Dysgeusia	21	<1	0	5	0	0
Headache	19	<1	0	13	0	0
Decreased weight	19	1	0	5	0	0
Dyspnea	18	4	0	9	1	<1
Arthralgia	16	1	0	16	0	0
Anemia	16	5	1	4	<1	<1
Epistaxis	15	0	0	1	0	0
Vomiting	14	<1	<1	11	<1	0
Peripheral edema	14	1	0	6	<1	0
Pyrexia	14	<1	0	6	<1	0
Aspartate aminotransferase level increased	13	3	<1	6	1	0
Constipation	13	<1	0	11	<1	0
Hyperglycemia	13	4	<1	2	<1	0
Pneumonitis	12	3	0	0	0	0
Thrombocytopenia	12	2	1	<1	0	<1
Asthenia	12	2	0	3	0	0
Alanine aminotransferase level increased	11	3	<1	3	2	0
Pruritus	11	<1	0	3	0	0
Insomnia	11	<1	0	8	0	0
Back pain	11	0	0	8	1	0

CDKs and Their Cyclin Regulatory Subunits



Aleem E, Arceci RJ. *Front Cell Dev Biol*. 2015;3:16.

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ESTABLISHED IN 1812 NOVEMBER 17, 2016 VOL. 375 NO. 20

Palbociclib and Letrozole in Advanced Breast Cancer

Richard S. Finn, M.D., Miguel Martin, M.D., Hope S. Rugo, M.D., Stephen Jones, M.D., Seock-Ah Im, M.D., Ph.D.,

Articles

Lancet Oncol 2016; 17: 425–39

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

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

Updated Results From MONALEESA-2, a Phase 3 Trial of First-line Ribociclib + Letrozole in Hormone Receptor-Positive (HR+), HER2-Negative (HER2–), Advanced Breast Cancer (ABC)

Abstract 1038

S, Campone
teaga CL,
sy J

ASCO 2017

MONARCH 2: Abemaciclib in Combination With Fulvestrant in Patients With HR+/HER2- Advanced Breast Cancer Who Progressed on Endocrine Therapy

Abstract 1000

Sledge GW, Toi M, Neven P, Sohn J, Inoue K, Pivot XB, Burdaeva ON, Okera M, Masuda N, Kaufman PA, Koh HA, Grischke E-M, Frenzel M, Lin Y, Barriga S, Smith IC, Bourayou N, Llombart A

ASCO 2017

DRUGS AVAILABLE IN CLINICAL PRACTICE

	FDA (USA)	EMA (EUROPE)	AIFA (ITALY)
Palbociclib	X	X	X
Ribociclib	X	X	/
Abemaciclib	X	/	/

(up date april 2018)

CDK 4 and 6 Inhibitors for the Treatment of HR-Positive, HER2-Negative Breast Cancer

Setting	Trial	Arm	Median PFS (mo)	Hazard Ratio (95% CI)
Endocrine sensitive No prior systemic treatment for advanced disease	PALOMA-2[a]	**Palbociclib** + letrozole	**24.8**	0.58 (0.46, 0.72); $P < .001$
		placebo + letrozole	14.5	
	MONALEESA-2[b,c]	**Ribociclib** + letrozole	**25.3**	0.57 (0.46, 0.70); $P = 9.63 \times 10^{-8}$
		placebo + letrozole	16.0	
	MONARCH-3[d,e]	**Abemaciclib** + anastrozole/letrozole	**Not reached**	0.54 (0.41, 0.72); $P = .000021$
		placebo + anastrozole/letrozole	14.7	
Endocrine resistant Relapse or disease progression on prior endocrine therapy	PALOMA-3[f,g]*	**Palbociclib** + fulvestrant	**11.2**	0.50 (0.40, 0.62); $P < .0001$
		placebo + fulvestrant	4.6	
	MONARCH-2[h]**	**Abemaciclib** + fulvestrant	**16.4**	0.55 (0.45, 0.68); $P < .001$
		placebo + fulvestrant	9.3	

*Disease progression while on or within 12 months after completion of adjuvant endocrine therapy, or while on or within 1 month after endocrine therapy in the advanced setting; 1 prior line of CT allowed

**Disease progression while on or within 12 months after completion of adjuvant endocrine therapy or while on first line endocrine therapy for metastatic disease

a. Finn RS, et al. *N Engl J Med*. 2016;375:1925-1936. b. Kisqali (ribociclib) PI. c. Hortobagyi G, et al. ASCO 2017; Abstract 1038. d. Di Leo A, et al. ESMO 2017. Abstract 2360. e. Goetz et al. *J Clin Oncol*. 2017;35:3638-3646. f. Ibrance (palbociclib) PI. g. Turner N, et al. SABCS 2016. Abstract P4-22-06. h. Sledge GW Jr, et al. *J Clin Oncol*. 2017;35:2875-2884.

CDK 4 and 6 Inhibitors: Differences in Target and Dosing Regime

- Palbociclib has equivalent CDK4/cyclin D3 and CDK6/cyclin D1 potency, while both ribociclib and abemaciclib are significantly more potent toward CDK4/cyclin D3 (ribociclib is 5-fold more potent, abemaciclib is 9-fold[a])
  - This may have important implications in terms of efficacy and toxicity

CDK K_i (nM)	Palbociclib	Ribociclib	Abemaciclib
CDK1/cyclinA_2	>1,400	>1,400	330 ± 90
CDK2/cyclinE_1	>2,500	>2,500	150 ± 60
CDK4/cyclinD_3	0.26 ± 0.03	0.53 ± 0.08	0.07 ± 0.01
CDK5/p35	>2,000	>2,000	86 ± 12
CDK6/cyclinD_1	0.26 ± 0.07	2.3 ± 0.3	0.52 ± 0.17
CDK7/cyclinH/MAT1	>2,000	>2,000	220 ± 10
CDK9/cyclinT_1	150 ± 10	190 ± 20	4.1 ± 1.3

Dosing:

- Palbociclib and ribociclib: intermittent; 3 weeks on, 1 week off, once daily[b,c]
- Abemaciclib: continuous regimen, once daily[c]

a. Chen P, et al. *Mol Cancer Ther*. 2016;15:2273-2281. b. Ibrance (palbociclib) PI 2017. c. Kisqali (ribociclib) PI 2017; d. Verzenio (abemaciclib) PI 2017.

Dosing

Palbociclib, Ribociclib: intermittent 3 weeks on 1 week off, once daily

Abemaciclib: continuous regimen once daily

Target

Palbociclib, Ribociclib target CDK 4 and 6 in similar way

Abemaciclib: target CDK 4 at a rate of 14 times higher versus CDK 6

Patients population (Goetz et al SABCS 2017, Abs G56-02)

Abemaciclib in combination with endocrine treatment offered more benefit in ORR and PFS i high-risk clinical characteristics such as liver metastases, progesterone receptors-negative tumors, high grade tumors, short DFS from adjuvant therapy

CDK 4 and 6 Inhibitors: Incidence of Neutropenia

- Hematological AEs are higher in all trials with CDK 4 and 6 inhibitors, compared to endocrine therapy alone
- The incidence of febrile neutropenia is low (<2%)[a-c]

	Palbociclib[a]		Ribociclib[b]		Abemaciclib[c,d]	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Neutropenia, %	79.5	56.1/10.4	74.3	49.7/9.6	87.7	22.3/4.6

a. Finn RS, et al. *N Engl J Med*. 2016;375:1925-1936; b. Hortobagyi G, et al. ASCO 2017. Abstract 1038; c. Di Leo A, et al. ESMO 2017. Abstract 2360; d. Goetz et al. *J Clin Oncol*. 2017;35:3638-3646.

Non-Hematological Side Effects Associated With CDK 4 and 6 Therapy

Non-hematological AEs are higher in all trials with CDK 4 and 6 inhibitors, compared to endocrine therapy alone[a-d]

- Mostly grade 1 and 2; rarely grade 3
- Nausea, vomiting, fatigue
- Alopecia: 15% to 30%, rarely above grade 1
- Diarrhea: frequent with abemaciclib, 9% grade 3/4

a. Finn RS, et al. *N Engl J Med*. 2016;375:1925-1936; b. Hortobagyi G, et al. ASCO 2017. Abstract 1038; c. Di Leo A, et al. ESMO 2017. Abstract 2360; d. Goetz et al. *J Clin Oncol*. 2017;35:3638-3646.

Other Side Effects Associated With CDK 4 and 6 Therapy

Liver enzyme elevation with ribociclib and abemaciclib[a-c]

- AST/ALT: 4%-7%, grade 3/4

Blood creatinine with abemaciclib[b,c]

- 10% to 20% with abemaciclib, rarely grade 3

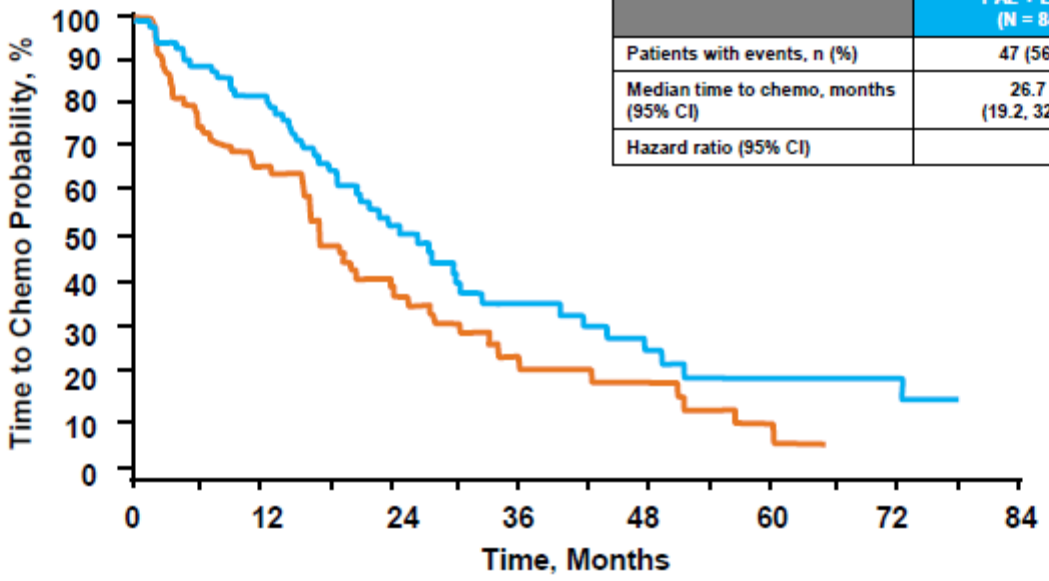
QTc interval prolongation with ribociclib[a]

- 3% grade 2
- 0.3% grade 3 (>500 ms prolongation)

a. Hortobagyi G, et al. ASCO 2017; Abstract 1038. b. Di Leo A, et al. ESMO 2017. Abstract 2360. c. Goetz et al. *J Clin Oncol.* 2017;35:3638-3646.

(Paloma-study: up date from ASCO 2017)

Time to Chemotherapy From Randomization



	PAL + LET (N = 84)	LET (N = 81)
Patients with events, n (%)	47 (56)	51 (63)
Median time to chemo, months (95% CI)	26.7 (19.2, 32.7)	17.7 (16.1, 24.4)
Hazard ratio (95% CI)	0.662 (0.445, 0.989)	

Finn RS, et al. *J Clin Oncol.* 2017;35(suppl): Abstract 1001.

(Paloma-study: up date from ASCO 2017)

Post-Study Systemic Therapies

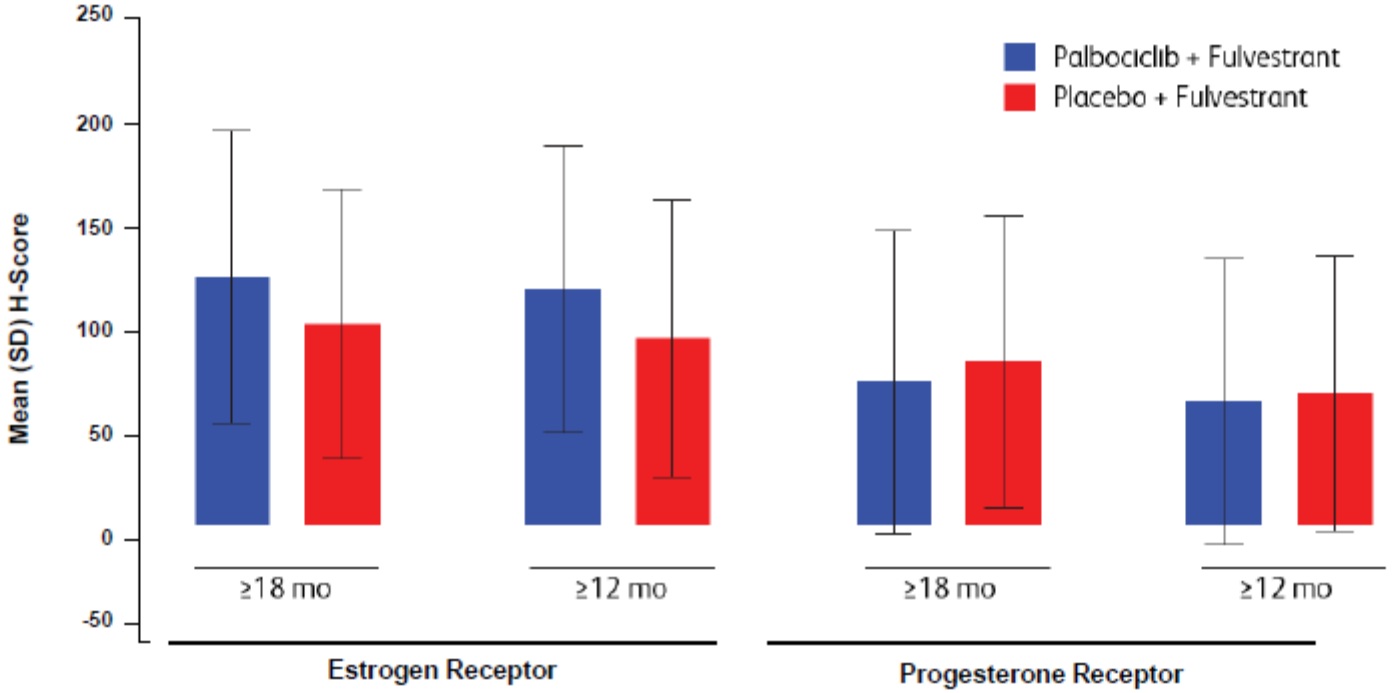
	PAL + LET [N = 80]	LET [N = 79]
Any post-study systemic therapy, n (%)	63 (83)	70 (89)
Post-study systemic therapy agents, n (%)		
Anti-hormonal therapy	50 (63)	58 (73)
Non-steroidal aromatase inhibitor	14 (18)	20 (25)
Steroidal aromatase inhibitor	21 (26)	28 (35)
Fulvestrant	27 (34)	34 (43)
Tamoxifen	11 (14)	17 (22)
Chemotherapy	47 (59)	51 (65)
Anthracyclines	15 (19)	22 (28)
Capecitabine	27 (34)	33 (42)
Gemcitabine	4 (5)	8 (10)
Taxanes	34 (43)	31 (39)
Vinorelbine	12 (15)	6 (8)
Other	19 (24)	19 (24)
mTOR inhibitor	12 (15)	13 (16)
Blinded therapy	2 (3)	5 (6)
Palbociclib	1 (1)	2 (3)

mTOR, mammalian target of rapamycin

Finn RS, et al. *J Clin Oncol.* 2017;35(suppl): Abstract 1001.

(Paloma 3-study: up date from ASCO 2017)

Quantitative ER and PR Results Among Long-Term Responders



Mean H-score by central laboratory analysis was calculated using the fluorescence *in situ* hybridization method. Error bars represent standard deviation.
ER, estrogen receptor; PR, progesterone receptor; SD, standard deviation

Cristofanilli M, et al. *J Clin Oncol*. 2017;35(suppl): Abstract 1050.

Conclusion: Hormone receptor status at baseline NOT PREDICTIVE for long-term benefit

Predicting Sensitivity to Palbociclib With Early Circulating Tumor DNA Dynamics in the PALOMA-3 Trial

Abstract 1018

O'Leary B, Hrebien S, Morden JP, Beaney M, Liu Y, Bartlett CH, Koehler M, Cristofanilli M, Garcia-Murillas I, Bliss J, Turner NC

Aims and Methods

Aims

- To assess whether early dynamic changes in the abundance of *PIK3CA* mutation would predict PFS in patients treated with palbociclib + fulvestrant.
- To assess clonal change in *ESR1* mutations in endocrine resistant breast cancer on treatment with palbociclib and fulvestrant.

Methods

- Plasma samples were prospectively collected in PALOMA-3 for ctDNA analysis at baseline, cycle 1 day 15 (D15) and end of treatment (EOT).
- Mutation status for both *PIK3CA* was assessed at baseline, day 15 and related to progression-free survival. Harrell's c-index was used to optimize a cut-off to predict PFS with early ctDNA dynamics.
- *ESR1* mutation status was assessed for clonal changes through treatment.

O'Leary B, et al. *J Clin Oncol*. 2017;35(suppl): Abstract 1018.

(Up date from ASCO 2017)

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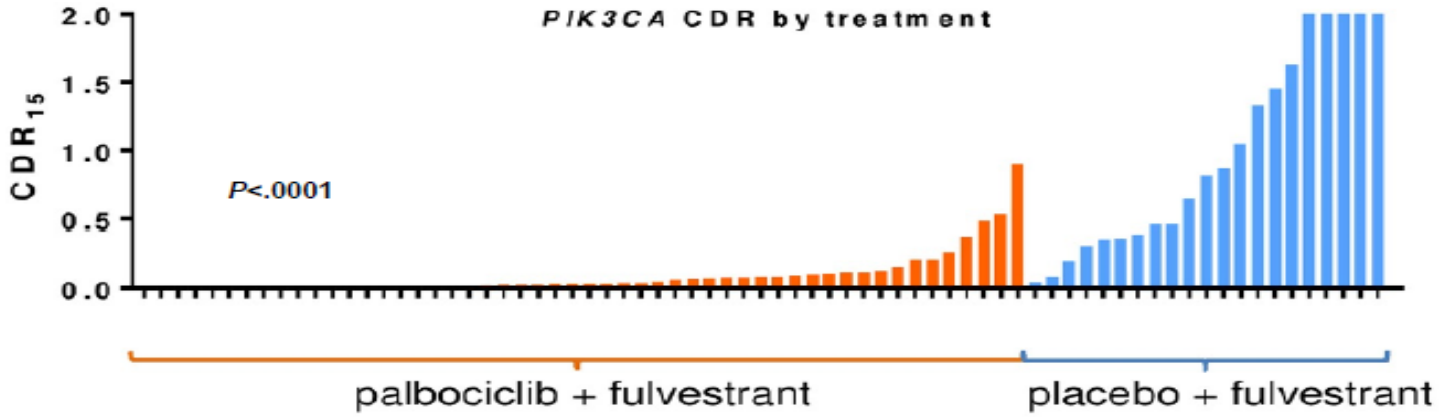
O'Leary B, et al. *J Clin Oncol.* 2017;35(suppl): Abstract 1018.

Palbociclib Suppresses ctDNA After 15 Days Treatment

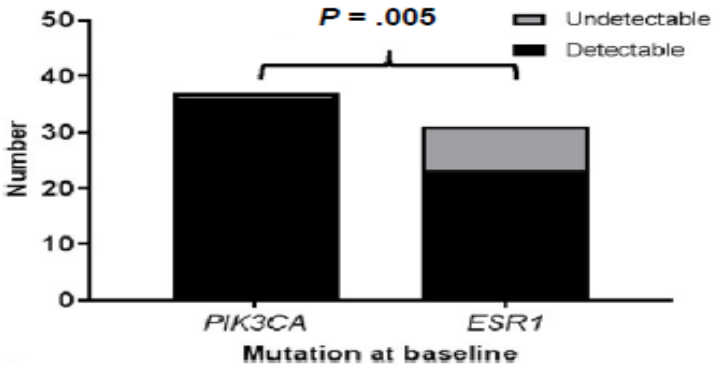
- The circulating DNA ratio (CDR) was defined as the ratio of aggregate day 15 mutant copies/ml relative to day 1 mutant copies/ml.



- Palbociclib + fulvestrant suppressed day 15 *PIK3CA* ctDNA levels to a greater extent than placebo + fulvestrant (*P*<.0001).

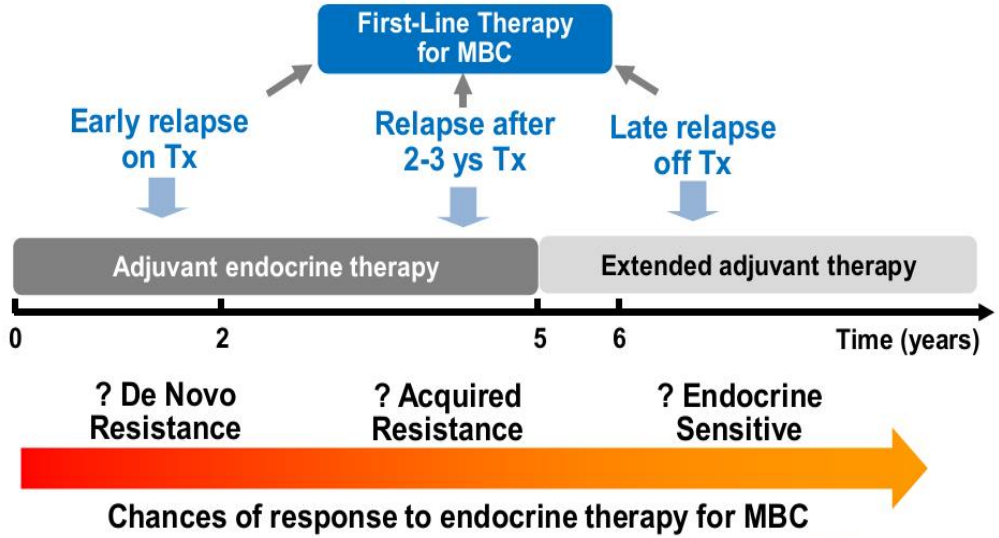
ESR1 Mutant Clones at End of Treatment

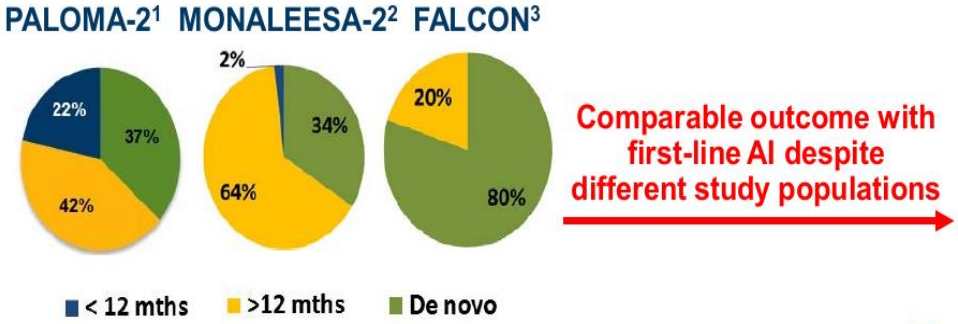
- *ESR1* mutant clones were more frequently undetectable at end of treatment (25.8% *ESR1* mutations undetectable 8/31, vs 2.6% for *PIK3CA* mutations, 1/38, *P* = .004).



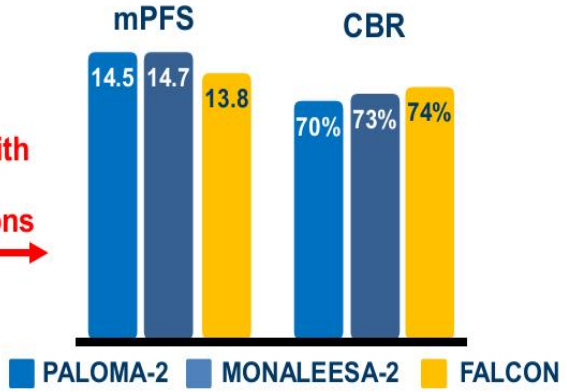
O'Leary B, et al. *J Clin Oncol*. 2017;35(suppl): Abstract 1018.

Defining Endocrine Sensitivity/Resistance With Adjuvant Treatment





Comparable outcome with first-line AI despite different study populations



AI, aromatase inhibitor; CBR, clinical benefit rate; MBC, metastatic breast cancer; mPFS, median progression-free survival; Tx, treatment

Finn RS, et al. *N Engl J Med.* 2016;375(20):1925-1936. Hortobagyi GN, et al. *N Engl J Med.* 2016;375(18):1738-1748. Robertson JFR, et al. *Lancet.* 2016;388(10063):2997-3005.

Abemaciclib for the Treatment of Brain Metastases (BM) Secondary to Hormone Receptor Positive (HR+), HER2-Negative Breast Cancer

Abstract 1019

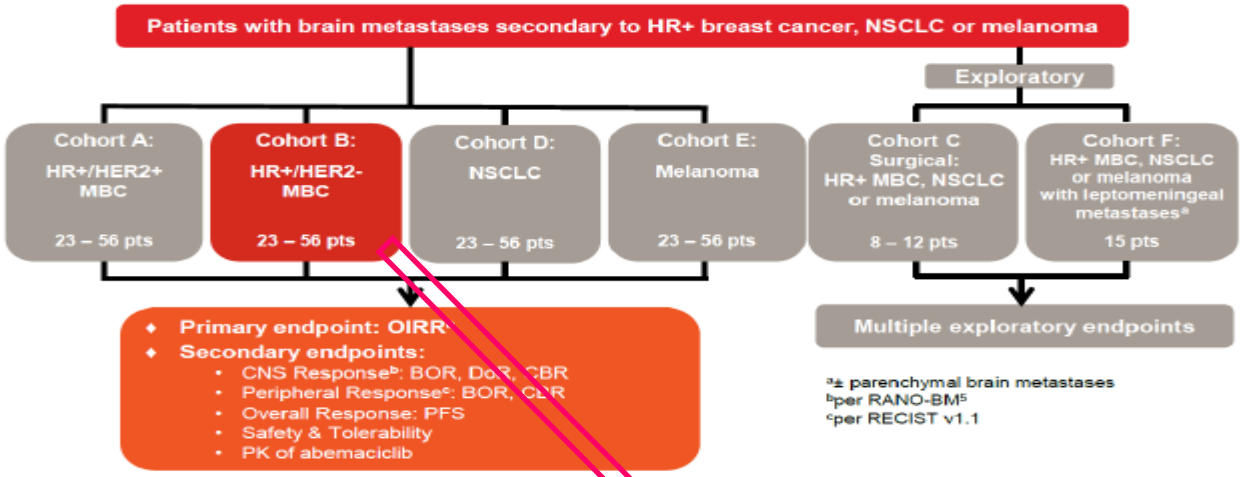
Tolaney SM, Lin NU, Thornton D, Klise S, Costigan TM, Turner PK, Anders CK

Background: Abemaciclib can crosss the blood-brain barrier

(ASCO 2017)

Study Design

An open-label phase II study of abemaciclib in patients with brain metastases secondary to HR+ breast cancer, NSCLC, or melanoma (NCT02308020)



BOR, best overall response; CBR, clinical benefit rate (CBR = CR + PR + SD ≥ 6 months); DoR, duration of response (DoR = CR+PR); pts, patients; OIRR, objective intracranial response rate (OIRR = CR + PR); PFS, progression-free survival; PK, pharmacokinetics; RANO-BM, response assessment in neuro-oncology brain metastases

Tolaney SM, et al. *J Clin Oncol.* **2017;35(suppl): Abstract 1019**

Key Inclusion Criteria for Part B

- Brain metastases secondary to HR+/HER2- breast cancer
- ≥1 new or not previously irradiated measurable metastatic brain lesion per RANO-BM criteria or a progressive previously irradiated metastatic brain lesion (per treating investigator)
- Completion of local and systemic therapies (except as outlined below) ≥14 days prior to initiation of abemaciclib
- May continue receiving endocrine therapy if peripheral disease has remained stable ≥3 months and CNS disease progression has occurred while on same therapy
- Stable or decreasing dose of corticosteroid ≥7 days prior to baseline Gd-MRI
- KPS ≥70
- Any number/type of prior therapies
- Peripheral metastatic disease is allowed but not required

KPS, Karnofsky performance status; Gd-MRI, gadolinium-enhanced magnetic resonance imaging

Tolaney SM, et al. *J Clin Oncol.* **2017;35(suppl): Abstract 1019**

Baseline Patient Characteristics

	N=23
Median age (range)	52.0 (35 - 69)
Age ≥ 65 years, n (%)	5 (21.7)
ER (+), n (%)	23 (100)
ER (+), PR (+), n (%)	15 (65.2)
ER (+), PR (-), n (%)	8 (34.8)
KPS, n (%)	
≥ 90	14 (60.9)
80	8 (34.8)
70	1 (4.3)

Baseline CNS Target Disease

	N=22[a]
Target CNS Lesions	
Number of lesions, median (range), n	1.5 (1 - 5)
1 lesion, n (%)	12 (54.5)
2 lesions, n (%)	5 (22.7)
≥ 3 lesions, n (%)	5 (22.7)
Sum LD, median (range), mm	27 (10 - 101)
Patients with Prior Therapy for Target CNS Lesions, n (%)	
Prior Surgery	1 (4.5)
Prior WBRT	10 (45.5)
Prior SRS	6 (27.7)

[a]One patient was enrolled without a target CNS lesion (< 5 mm in perpendicular diameter).
SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy.

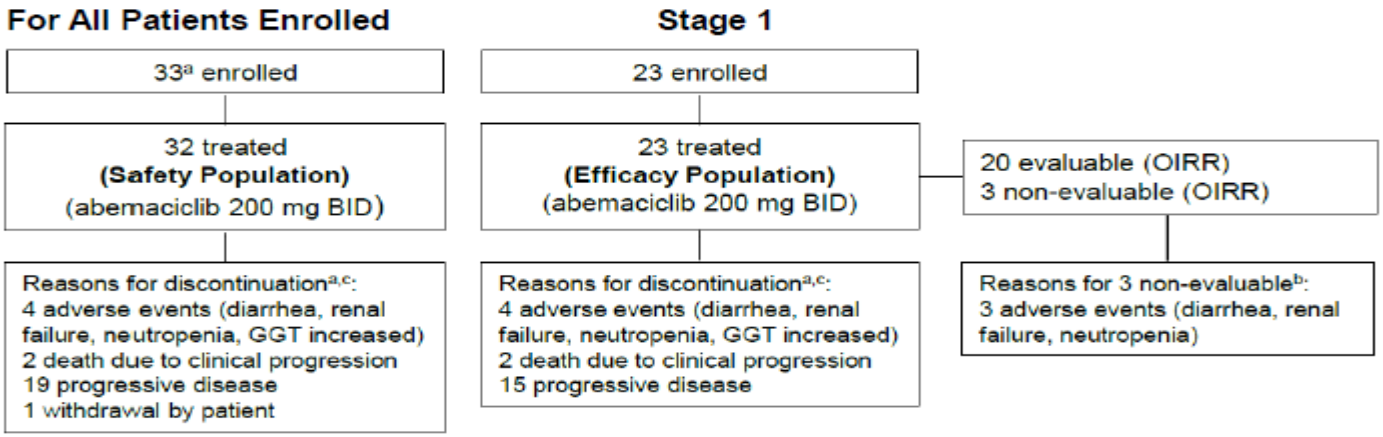
RANO-BM Criteria

RANO-BM, response assessment in neuro-oncology brain metastases

Criterion	CR	PR	SD	PD
Target lesions	None	≥30% decrease in sum LD relative to baseline	<30% decrease relative to baseline but <20% increase in sum LD relative to nadir	≥20% increase in sum LD relative to nadir. In addition to relative increase of 20%, ≥1 lesion must increase by absolute value ≥5 mm*

Results

Patient Disposition in Part B

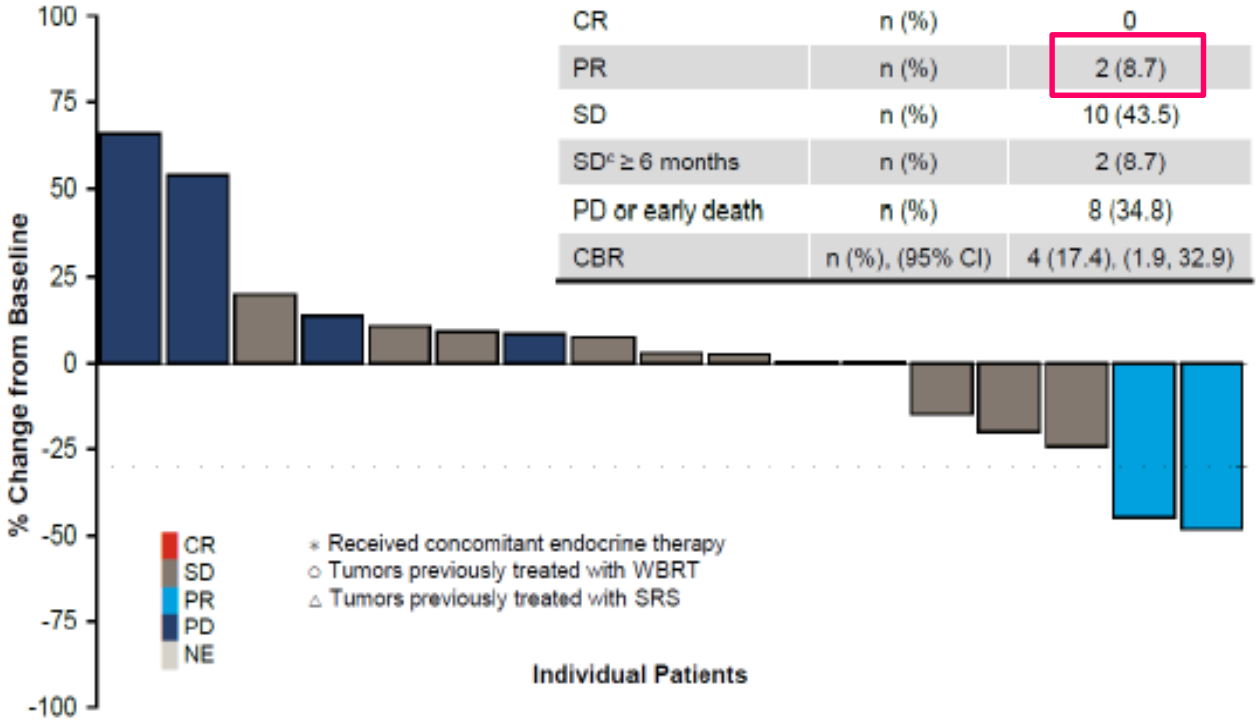


[a]At the time of data cut-off on 11OCT2016
[b]Patients were non-evaluable if discontinued due to adverse events prior to post-baseline tumor assessment.
[c]Includes patients who were off treatment as well as the patients who were enrolled but never treated
GGT, gamma glutamyl transferase

The efficacy population includes Stage 1 patients only.
The safety population included all patients enrolled (stage 1 + stage 2) who had received at least one dose of treatment at the time of the analysis.

CNS Response[a] Summary[b]

Efficacy Population Patients with Response		N=23
OIRR	n (%), (95% CI)	2 (8.7), (0.0, 20.2)
CR	n (%)	0
PR	n (%)	2 (8.7)
SD	n (%)	10 (43.5)
SD[c] ≥ 6 months	n (%)	2 (8.7)
PD or early death	n (%)	8 (34.8)
CBR	n (%), (95% CI)	4 (17.4), (1.9, 32.9)



*Response criteria per RANO-BM; [b]6 patients had no post-baseline tumor measurements and therefore were not included in this waterfall plot.
[c]Patients with SD ≥ 6 months are included in the number of patients with SD.*

Overall[b] median PFS: 4.04 months

Clinical Trials Performed in U.O Oncologia - Negrar

MONARCH 3 - Protocol 13Y-MC-JPBM (b)

A randomized placebo-controlled, phase III study of nonsteroidal aromatase inhibitors (anastrozoleor letrozole) plus LY2835219, a CDk 4/6 inhibitor or placebo in postmenopausal women with hormone receptor-positive, HER2-negative, locoregionally recurrent or metastatica breast cancer with no prior systemic therapy in this disease setting.

Primary objective: to compare treatment with LY2835219 plus NSAI therapy vs placebo+NSAI in PFS

Next-MONARCH – Protocol 13Y-MC-JPCG

A randomized open-label, phase 2 study of abemaciclib plus tamoxifen or abemaciclib alone in women with previously treated hormone receptor-positive, metastatico breast cancer, HER2-negative.

Primary objective: to evaluate the efficacy in term of PFS in patients with MBC for abemaciclib 150q12H+TAM, Abemaciclib 150Q12H, Abemaciclib 200q12H+loperamide

COMPLEEMENT 1 – LEE011 (ribociclib)

An open-label, multicentric, phase IIIb study to assess the safety and efficacy of ribociclib (LEE011) in combination with letrozole for the treatment of **men** and **pre**/postmenopausal women with hormone receptor-positive HER2-negative advanced breast cancer with no prior therapy for advanced disease .

Primary objective: to evaluate safety and efficacy in men and pre/postmenopausal women in TTP, ORR, CBR.

BioItalee – CLEE011AIT01

A phase IIIb, open-label, local multicenter study of the molecular features of postmenopausal women with hormone receptor-positive HER2-negative advanced breast cancer on first-line treatment with ribociclib and letrozole

Primary objective: to identify circulating tumora Dna (ctDNA) alterations, how to evolve, and evaluate their possible association with clinical outcome.