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8TH ANNUAL PUERTO RICO WINTER CANCER SYMPOSIUM 2019
"Immunotherapy and Targeted Therapy Moving Forward in the Oncology Practice"

Hormonal and Targeted Therapy in the Management of ER+ Metastatic Breast Cancer

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Disclosure Information

I have the following financial relationships to disclose:

Consultant/Advisory Boards/Education: Roche, Merck, Novartis and Astra-Zeneca

Outline

- Overview
- Hormonal Therapy
- M-THOR inhibitors
- CDK4/6 inhibitors
- PI3K/AKT inhibitors
- Conclusions

Current Treatment of Advanced Hormone Receptor Positive (HR+) HER2- Breast Cancer

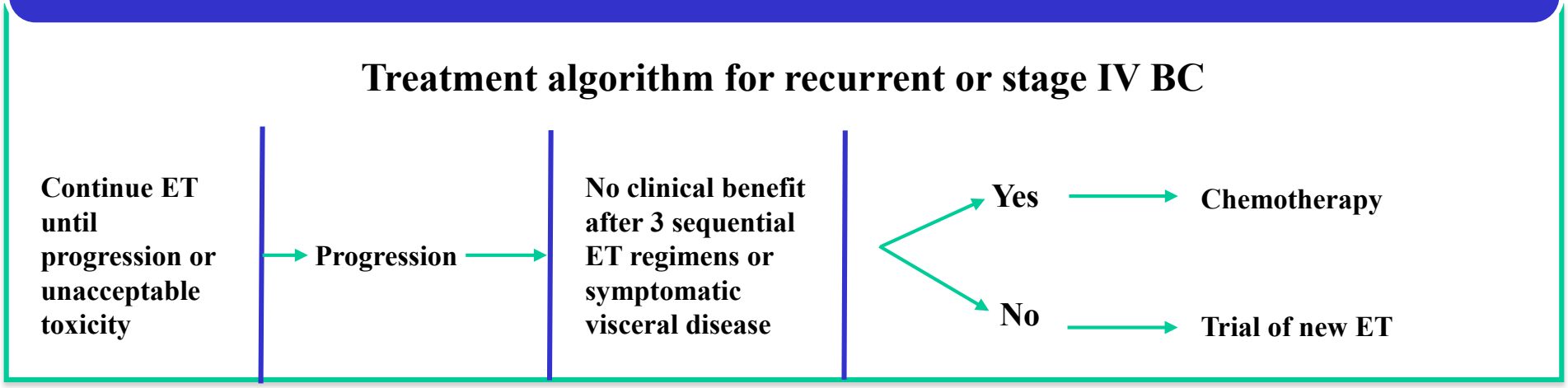
- Nearly 75% of patients have invasive breast cancers are hormone receptor positive (HR^+)
- Endocrine therapy is the standard of care for patients with HR^+ breast cancer, recommended by national and international guidelines
- Hormone therapy plus minus targeted therapy is as effective as (or more effective than) chemotherapy for patients with HR+ MBC
- Sequential endocrine therapy may add years of high quality life to patients with ER+ MBC
- Several developments in the past 5 years offer promising treatment options and better care for patients with HR+ MBC,

Systemic Treatment for Patients with HR+, HER2− MBC

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend 3 lines of consecutive ET for patients with HR+ MBC without visceral symptoms.

- FDA-approved ETs or combination therapies include tamoxifen, goserelin plus tamoxifen, anastrozole, letrozole, exemestane, exemestane + everolimus, ribociclib + letrozole or fulvestrant, palbociclib + letrozole or fulvestrant, abemociclb+/- fulvestrant or letrozole

Evidence suggests that patients derive diminishing benefits with each additional line of therapy.

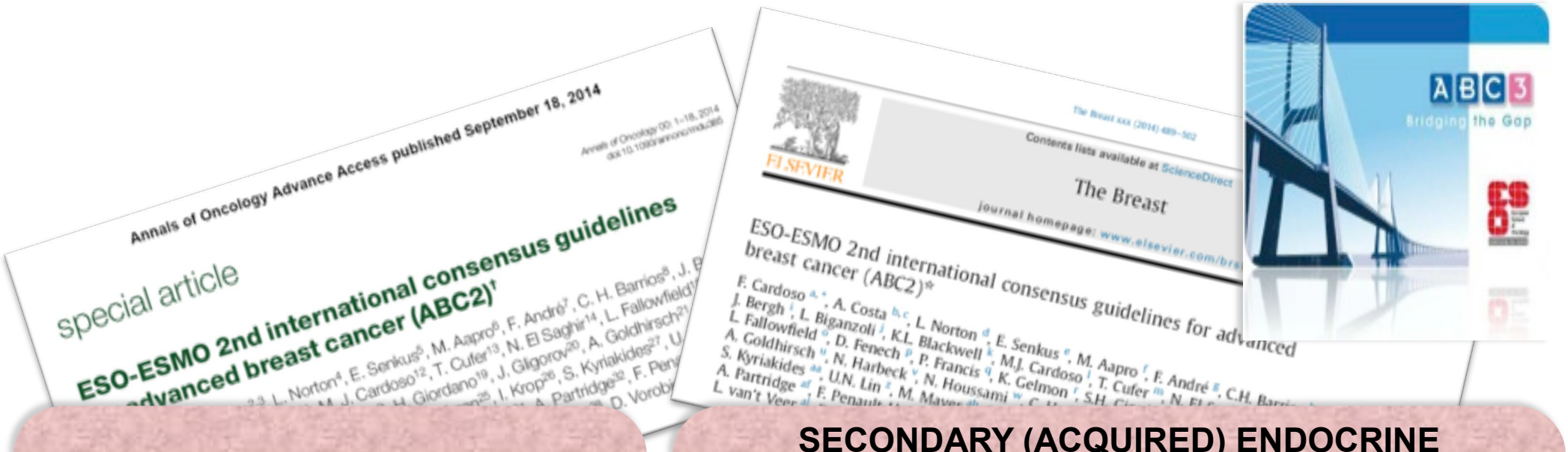


Are there preferred combinations or single agents and sequence of endocrine therapies?

ET = endocrine therapy; HR = hormone receptor; HER = human epidermal growth receptor; ABC = advanced breast cancer.

The NCCN Clinical Practice Guidelines in Oncology. Breast Cancer V3. 2017. December 15, 2017

Definitions of Endocrine Resistance in ER+ MBC



PRIMARY ENDOCRINE RESISTANCE Relapse while on the first 2 years of adjuvant ET, or PD within first 6 months of 1st line ET for MBC, while on ET

SECONDARY (ACQUIRED) ENDOCRINE RESISTANCE
Relapse while on adjuvant ET but after the first 2 years, or relapse within 12 months of completing adjuvant ET,
or PD ≥ 6 months after initiating ET for MBC, while on ET

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New Trials of Hormone Therapy Alone in First-Line Advanced Breast Cancer

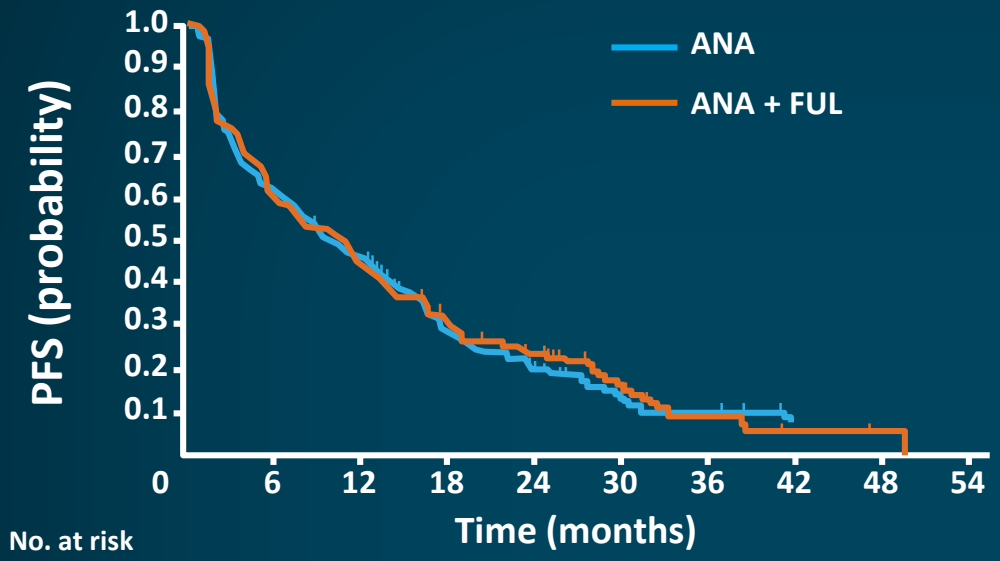
Improving upon AIs as standard of care as 1st-line endocrine therapy for HR+ MBC

Recent 1st Line Studies:

- Combination Endocrine Rx (Fulvestrant + AI) (FACT; SWOG-0226)
- Anastrozole versus Fulvestrant (FALCON)
- Addition of growth factor tyrosine kinase inhibitors (M-THOR and PI3K inhibitors, TAMRAD, BOLERO-2, BELLE 2-3, SANDIPER)
- Addition of CDK 4/6 inhibitors (PALOMA-2 and 3; MONALEESA-2, 3, and 7 and Monarch-2 and 3)

First-Line Anastrozole ± Fulvestrant ER+ MBC

FACT[1]: TTP

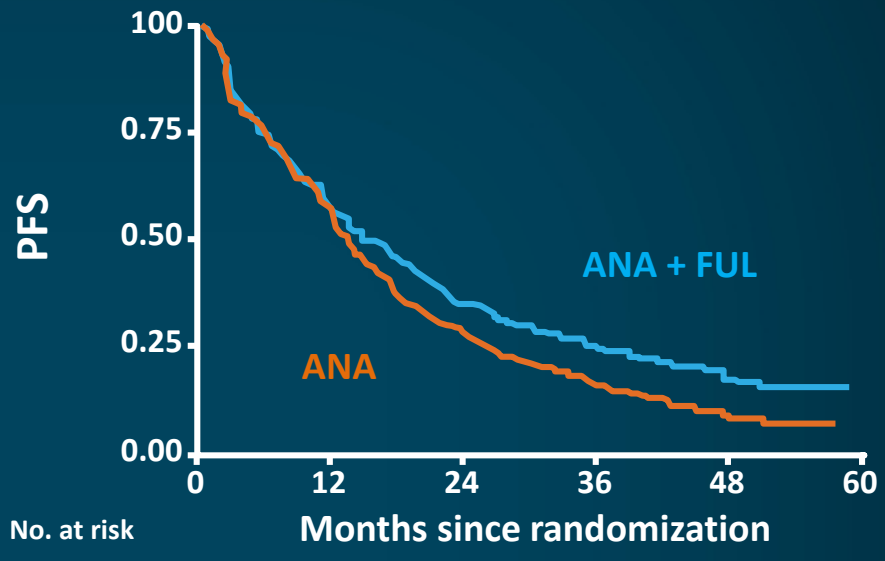


No. at risk										
ANA	256	148	108	57	31	16	10	5	4	1
ANA + FUL	258	149	107	55	40	20	6	2	1	0

	ANA + FUL (n = 258)	ANA (n = 256)
Patients with progression, no. (%)	200 (77.5)	200 (78.1)
Median TTP in months	10.8	10.2

Primary TTP analysis (log-rank test)
HR = 0.99 (95% CI, 0.81–1.20), *P*=0.91

SWOG 0226[2]: PFS



No. at risk						
ANAf	349	199	114	53	21	8
ANA + FUL	345	193	92	39	11	3

	Events	Median PFS (95% CI)
Combination	268	15.0 (13.2–18.4)
ANA	297	13.5 (12.1–15.1)

HR = 0.80 (95% CI, 0.68–0.94)
P=0.007 by stratified log-rank test

ER = estrogen receptor; MBC = metastatic breast cancer; ANA = anastrozole; FUL = fulvestrant; TTP = time to progression; SWOG = Southwest Oncology Group; PFS = progression-free survival; HR = hazard ratio (in reporting risk); CI = confidence interval.

1. Bergh J et al. *J Clin Oncol*. 2012;30:1919-1925. 2. Mehta RS et al. *N Engl J Med*. 2012;367:435-444.

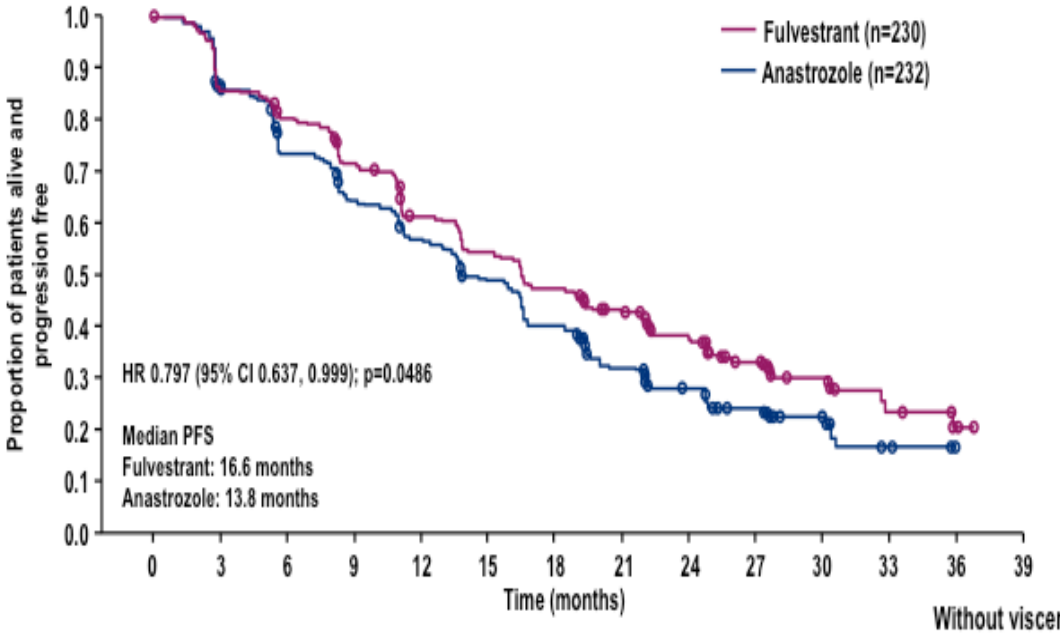
FALCON: (*F*ulvestrant and *A*nastrozo*L*e *CO*mpared in Hormonal Therapy-*N*aïve Advanced BC)

- Randomized, double-blind, parallel-group, international, multicenter study
- Randomization of 450 patients was planned to achieve 306 progression events; if true PFS HR was 0.69 this would provide 90% power for statistical significance at the 5% two-sided level (log-rank test).

BC = breast cancer; PgR = progesterone receptor; HER = human epidermal growth receptor; PO = by mouth; ORR = objective (or overall) response rate; CBR = clinical benefit rate; DoR = duration of response; EDoR = expected DoR; DoCB = duration of clinical benefit; EDoCB = expected DoCB; HRQoL = health-related quality of life; FACT-B = Functional Assessment of Cancer Therapy for BC; TOI = Trial Outcome Index.

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

FALCON Trial: Anastrozole vs Fulvestrant

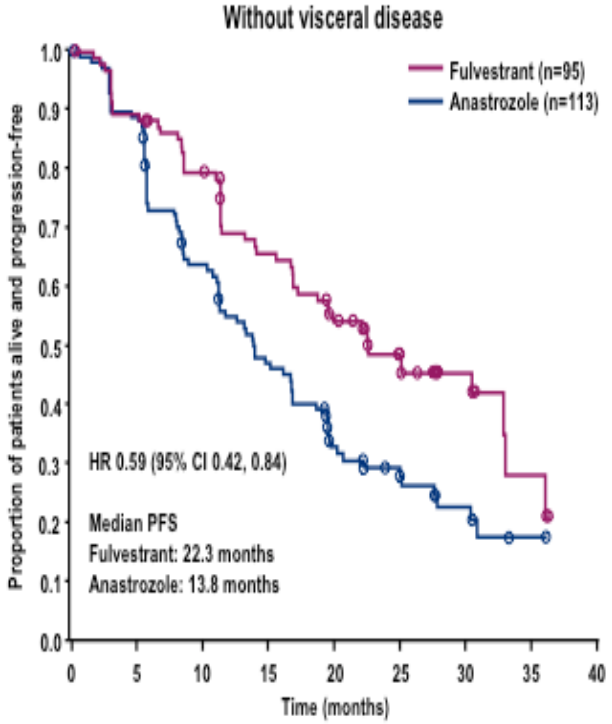


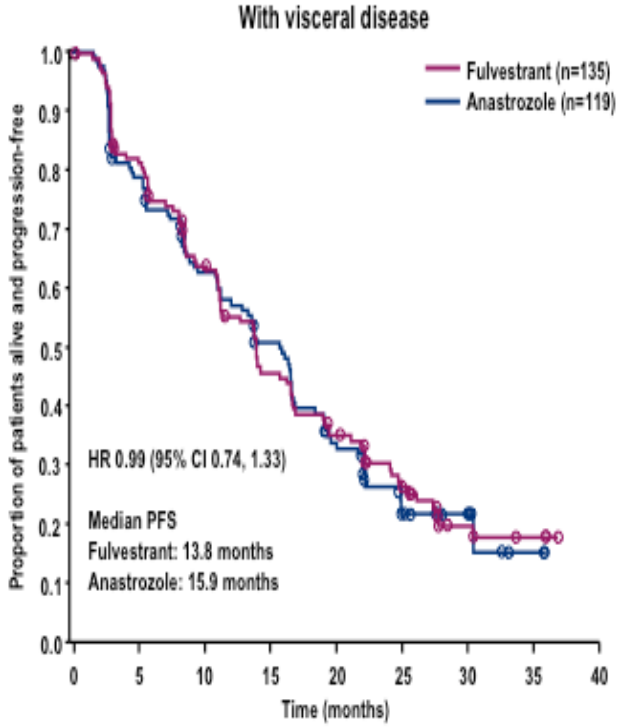
Forest plot for subset analysis

- No difference among predefined subsets EXCEPT visceral disease
  - HR = 0.992 (visceral disease) vs 0.592 (non-visceral disease)

No difference in OS to date

Post-hoc interaction test *P* <.01; a circle represents a censored observation





Robertson JFR et al, Lancet Oncology 2016

Major Challenge in Endocrine Resistance

- Approximately 30-50% of patients with HR^+ advanced breast cancer do not respond to initial endocrine therapy.
- The majority (if not all) of patients with HR^+ advanced breast cancer will ultimately progress despite endocrine therapy.

Bedard PL, et al. *Breast Cancer Res Treat*. 2008;108(3):307-317.

Approaches to Overcoming Resistance to Endocrine Therapy

- **Alterations of downstream signaling pathways such as PI3K, (mTOR and PI3K inhibitors)**

- Alterations of the cell cycle machinery (CDK inhibitors)

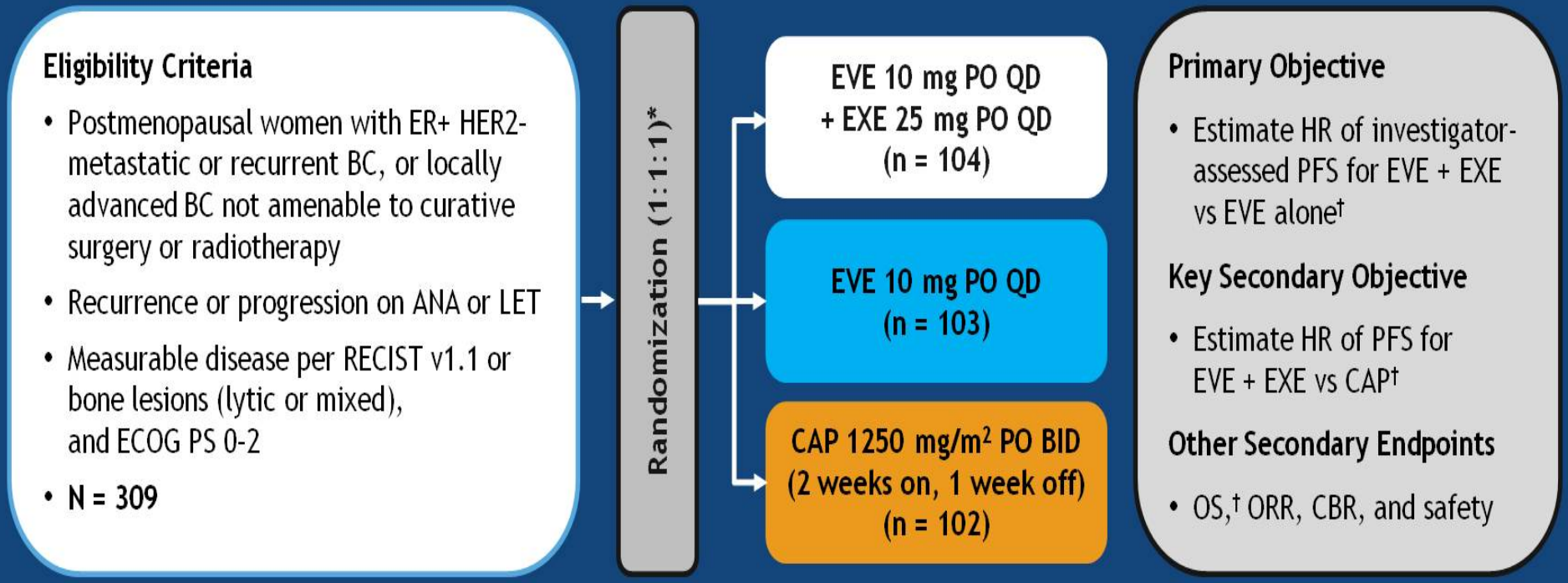
Randomized Trials of mTOR Inhibitors and Endocrine Therapy for Patients with ER+ MBC

Study	Agents	No. of patients	% RR/CBR	PFS in mos	HR (95% CI)	*P*
TAMRAD	Tamoxifen	57	13/42.1	4.5		
	Tamoxifen + everolimus	54	14/61.1	8.6	0.54 (0.35-0.81)	0.002
HORIZON	Letrozole	556	27/-	9.0		
	Letrozole + Temsirolimus	556	29/-	8.9	0.90 (0.76-1.07)	0.25
BOLERO-2	Exemestane	239	1.7/26.4	3.2		
	Exemestane + Everolimus	485	12.6/51.3	7.8	0.45 (0.38-0.54)	<0.0001

Bachelot T, et al., *J Clin Oncol* 30(22):2718-24, 2012; Wolff AC, et al., *J Clin Oncol* 31(2):195-202, 2013; Baselga J, et al., *NEJM* 366(6):520-9, 2012

Randomized, Open-Label, Phase II Study

- BOLERO-6 randomized 309 patients to receive EVE + EXE (n = 104), EVE alone (n = 103), or CAP (n = 102)



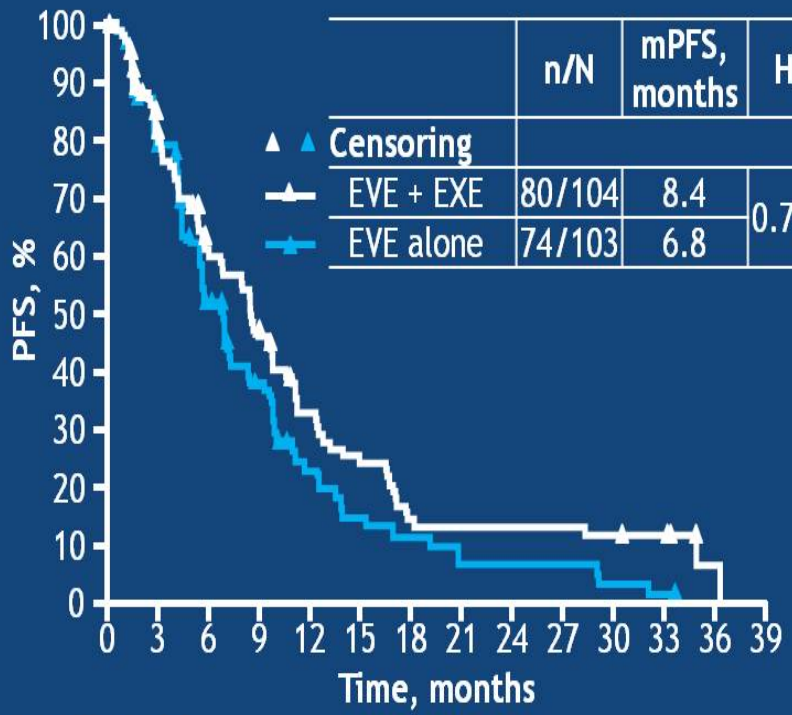
- BOLERO-6 was not powered to perform statistical comparisons between arms

*Stratified by presence or absence of visceral disease (lung, liver, heart, ovary, spleen, kidney, adrenal gland, malignant pleural or pericardial effusion, or malignant ascites; †Stratified multivariate Cox regression models were adjusted on treatment and the following prognostic and baseline covariates where imbalances between arms were observed: bone-only lesions (yes vs no); prior chemotherapy (yes vs no); ECOG PS (0 vs 1-2); organs involved (2 vs 1, and ≥3 vs 1); race (Caucasian vs non-Caucasian); age (<65 vs ≥65 years).
ANA, anastrozole; BID, twice daily; CBR, clinical benefit rate; ECOG PS, Eastern Cooperative Oncology Group performance status; LET, letrozole; NSAI, nonsteroidal aromatase inhibitor; ORR, overall response rate; OS, overall survival; PO, oral administration; QD, once daily; RECIST, Response Evaluation Criteria In Solid Tumors.

http://jamanetwork.com/journals/jamaoncology/fullarticle/10.1001/jamaoncol.2018.2262

Primary Objective
Estimated HR of PFS for EVE + EXE vs EVE alone

EVE + EXE offers a PFS benefit vs EVE alone



	n/N	mPFS, months	HR* (90% CI)
EVE + EXE	80/104	8.4	0.74 (0.57-0.97)
EVE alone	74/103	6.8	

Patients still at risk

EVE + EXE	104	73	52	39	26	19	11	10	10	10	9	5	1	0
EVE alone	103	66	40	26	14	9	7	4	4	4	2	1	0	0

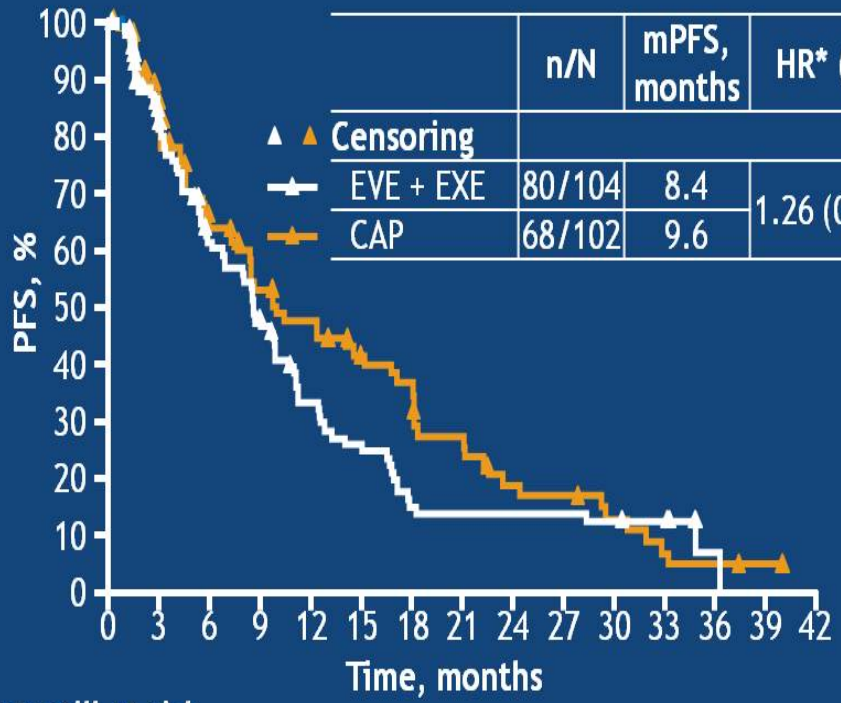
- Estimated HR of PFS for EVE + EXE vs EVE alone was 0.74 (90% CI 0.57-0.97)
- Censored for initiating new antineoplastic therapies:
  - EVE + EXE arm, 9%
  - EVE alone arm, 18%
- A stratified multivariate Cox regression model accounting for baseline imbalances and known prognostic factors gave **a consistent HR (0.73; 90% CI 0.56-0.97)** for EVE + EXE vs EVE alone

*EVE + EXE vs EVE alone (obtained from a stratified Cox model).
mPFS, median progression-free survival.

http://jamanetwork.com/journals/jamaoncology/fullarticle/10.1001/jamaoncol.2018.2262

Key Secondary Objective
Estimated HR of PFS for EVE + EXE vs CAP

CAP may have been favored by baseline imbalances and potential informative censoring



	n/N	mPFS, months	HR* (90% CI)
EVE + EXE	80/104	8.4	1.26 (0.96-1.66)
CAP	68/102	9.6	

Patients still at risk

EVE + EXE	104	73	52	39	26	19	11	10	10	10	9	5	1	0	0
CAP	102	68	48	38	33	26	19	14	10	9	6	3	2	1	0

- Estimated HR of PFS for EVE + EXE vs CAP was 1.26 (90% CI 0.96-1.66)
- Censored for initiating new antineoplastic therapies:
  - EVE + EXE arm, 9%
  - CAP arm, 20%
- A stratified multivariate Cox regression model accounting for baseline imbalances and known prognostic factors gave **a HR of 1.15 (90% CI 0.86-1.52)** for EVE + EXE vs CAP

*EVE + EXE vs CAP (obtained from a stratified Cox model).

http://jamanetwork.com/journals/jamaoncology/fullarticle/10.1001/jamaoncol.2018.2262

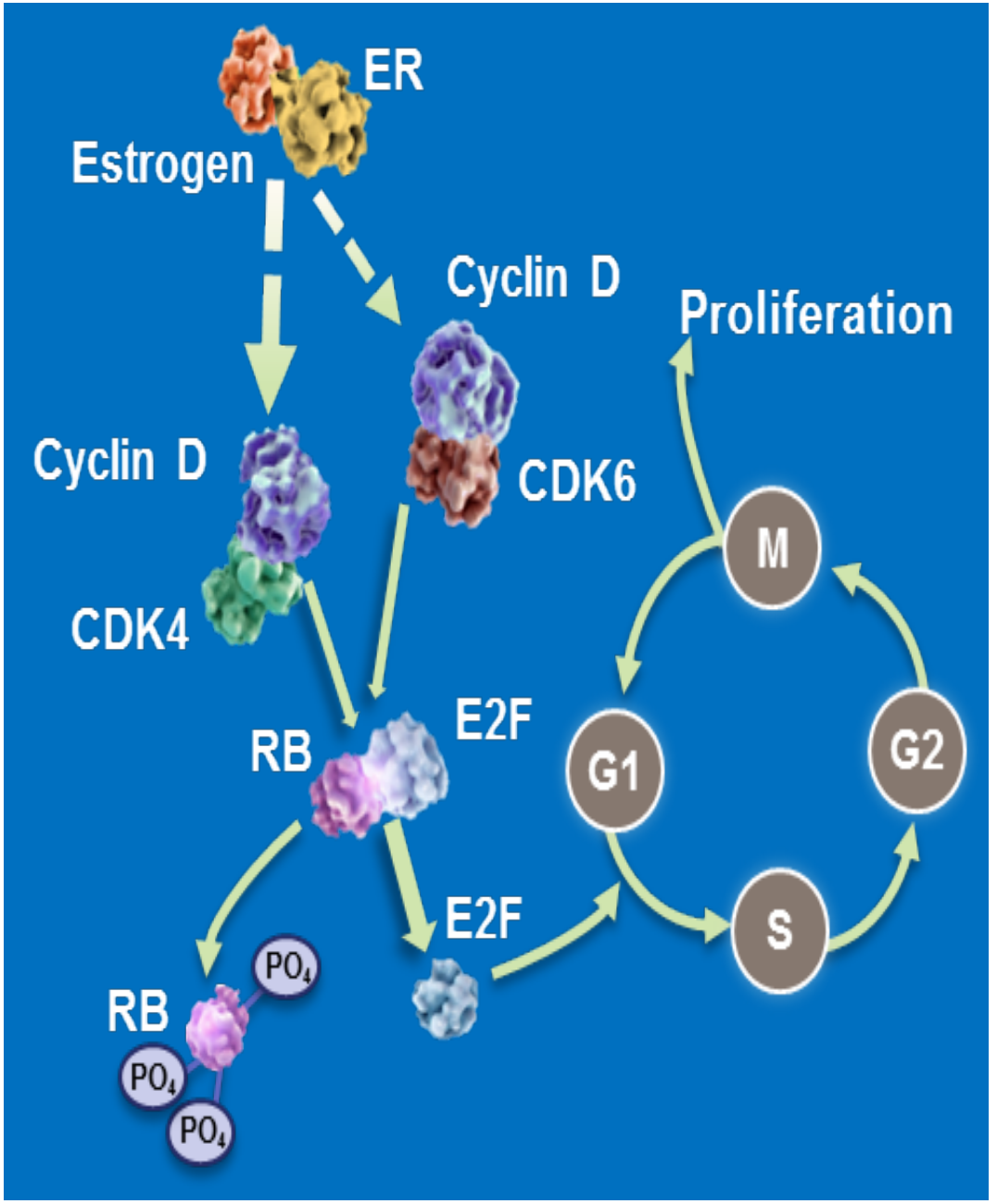
Approaches to Overcoming Resistance to Endocrine Therapy

- Alterations of downstream signaling pathways such as PI3K, (mTOR and PI3K inhibitors)

- **Alterations of the cell cycle machinery (CDK inhibitors)**

CDK4/6 in HR+ Breast Cancer

- HR+ breast cancer growth is dependent on cyclin D1, a direct transcriptional target of ER
- Cyclin D1–CDK4/6 complexes initiate Rb hyperphosphorylation
- Rb hyperphosphorylation results in it's inactivation, which allows the cell to progress from G1 to S-phase[1]
- Short-term inhibition of CDK4 & 6 leads to G1 arrest (that rebounds on withdrawal)[2]



[1]Hosford Pharmgenomics Pers Med 2014; [2]Gelbert *Invest New Drugs* 2014
Figure adapted from Jerusalem ASCO 2018

Status of CDK4/6 Inhibitors in Development

	Palbociclib (Ibrance®, Pfizer)	Ribociclib (Kisqali®, Novartis)	Abemaciclib (Verzenio™, Eli Lilly)
Potency (IC_{50})	CDK4: 9–11 nM CDK6: 15 nM	CDK4: 10 nM CDK6: 39 nM	CDK4: 2 nM CDK6: 10 nM
Dose/schedule	125 mg daily, 3 weeks on/1 off	600 mg daily 3 weeks on/1 off	Combination:150 mg BID Monotherapy: 200 mg BID Continuous
Completed Phase III trials	1st line: PALOMA-2 2nd line: PALOMA-3	1st line: MONALEESA-2-3 MONALEESA-7 2nd line: MONALEESA-3	1st line: MONARCH-3 1st or 2nd line: MONARCH-2
FDA approval status	2015: 1st line (with letrozole) 2016: 2nd line (with fulvestrant)	2017: 1st line (with letrozole) 2018: 1st and 2nd (with fulvestrant)	2017: 2nd line (with fulvestrant) Single agent post-ET and chemo

BID = twice a day; Chemo = chemotherapy.

Palbociclib (Ibrance®) prescribing information (PI), 2017. Ribociclib (Kisqali®) PI, 2017. Abemaciclib (Verzenio™) PI, 2017.

Randomized Trials in First-Line HR+ MBC

Study	No. of patients	ORR	CBR	mPFS in mos (95% CI)	HR	*P*
PALOMA-1						
- Letrozole	81	33 (39)	58	10.2 (5.7-12.6)	0.488	0.0004
- Letrozole + palbociclib	84	43 (56)	81	20.2 (13.8-27.5)	(0.319-0.748)	
PALOMA-2						
- Letrozole + placebo	222	35 (44)	71	14.5 (12.9-17.1)	0.58	<0.0001
- Letrozole + palbociclib	444	42 (55)	84	24.8 (22.1-NR)	(0.46-0.72)	
MONALEESA-2						
- Letrozole + placebo	334	28 (37)	72	14.7 (13.0-16.5)	0.556	0.00000329
- Letrozole + ribociclib	334	41 (53)	80	NR (19.3-NR)	(0.429-0.720)	
MONALEESA-3						
- Fulvestrant + placebo	238	N/A	N/A	18.3 (N/A)	0.577	N/A
- Fulvestrant + ribociclib	129	N/A	N/A	NR (N/A)	(0.415-0.802)	
MONALEESA-7						
- Tamoxifen/NSAI + GnRH + placebo	337	30 (36)	67	13.0 (11.0-16.4)	0.553 (0.441-0.694)	0.000000098
- Tamoxifen/NSAI + GnRH + ribociclib	335	41 (51)	80	23.8 (19.2-NR)		
MONARCH-3						
- NSAI + placebo	165	35 (44)	72	14.7	0.543	0.000021
- NSAI + abemaciclib	328	48 (59)	78	NR	(0.409-0.723)	

Finn RS, et al. Lancet Oncol, 16(1):25 - 35, 2015; Finn RS, et al. NEJM 375(20):1925-36, 2016; Hortobagyi GN, et al. NEJM 375(18):1738-48, 2016; Goetz MP, et al. *J Clin Oncol* 35(32):3638-3646, 2017; Tripathy D, et al. SABCS 2017 GS2-05

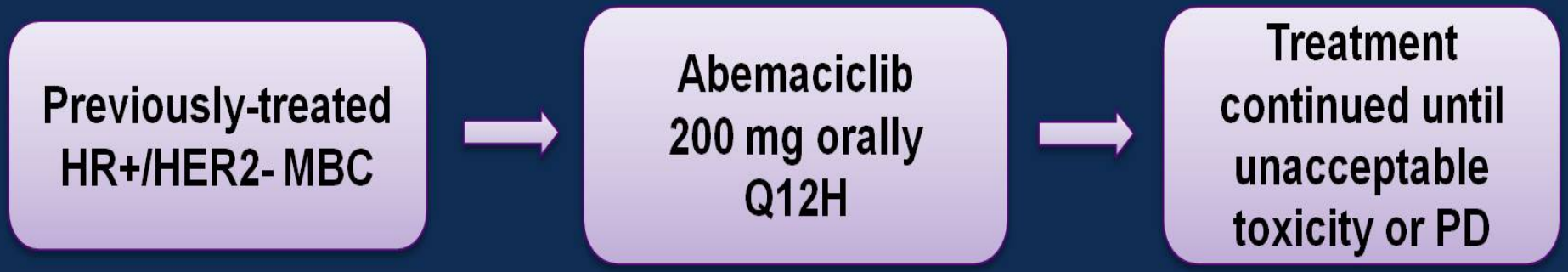
Randomized Trials with cdk4/6-Inhibitors in Pre-Treated Metastatic, HR+ Breast Cancer

Study	No. of patients	ORR	CBR	mPFS in mos (95% CI)	HR	*P*
Second-Line Metastatic Breast Cancer						
PALOMA-3						
- Fulvestrant + placebo	174	6.3	19.0	3.8 (3.5-5.5)	0.422 (0.318-0.560)	<0.000001
- Fulvestrant + Palbociclib	347	10.4	34.0	9.2 (7.5-NR		
MONARCH-2						
- Fulvestrant + placebo	223	16.1	56.1	9.3	0.553 (0.449-0.681	<0.0000001
- Fulvestrant + Abemaciclib	446	35.2	72.2	16.4		
MONALEESA-3						
- Fulvestrant + placebo	109	N/A	N/A	9.1	0.57	N/A
- Fulvestrant + Ribociclib	236	N/A	N/A	14.6	0.42-0.74	
Third-Line Metastatic Breast Cancer and Beyond						
MONARCH-1	132	19.7	42.4	6.0 (4.2-7.5)	N/A	N/A

Turner NC., et al. NEJM 373(3):209-19, 2015; Sledge GW Jr. Et al. *J Clin Oncol* 35(25):2875-2884, 2017; Dickler MN, et al. *Clin Cancer Res* 23(17):5218-5224, 2017; Slamon DJ, ASCO 2018

Special Clinical Situation
CDK 4/6 Single Agent Therapy in ER+ HER-2 normal Refractory Metastatic Breast Cancer, brain metastasis and Elderly

MONARCH 1: Phase 2 Study Design



Primary objective

To evaluate abemaciclib with respect to confirmed objective response rate based on investigator assessment (per RECIST v1.1)

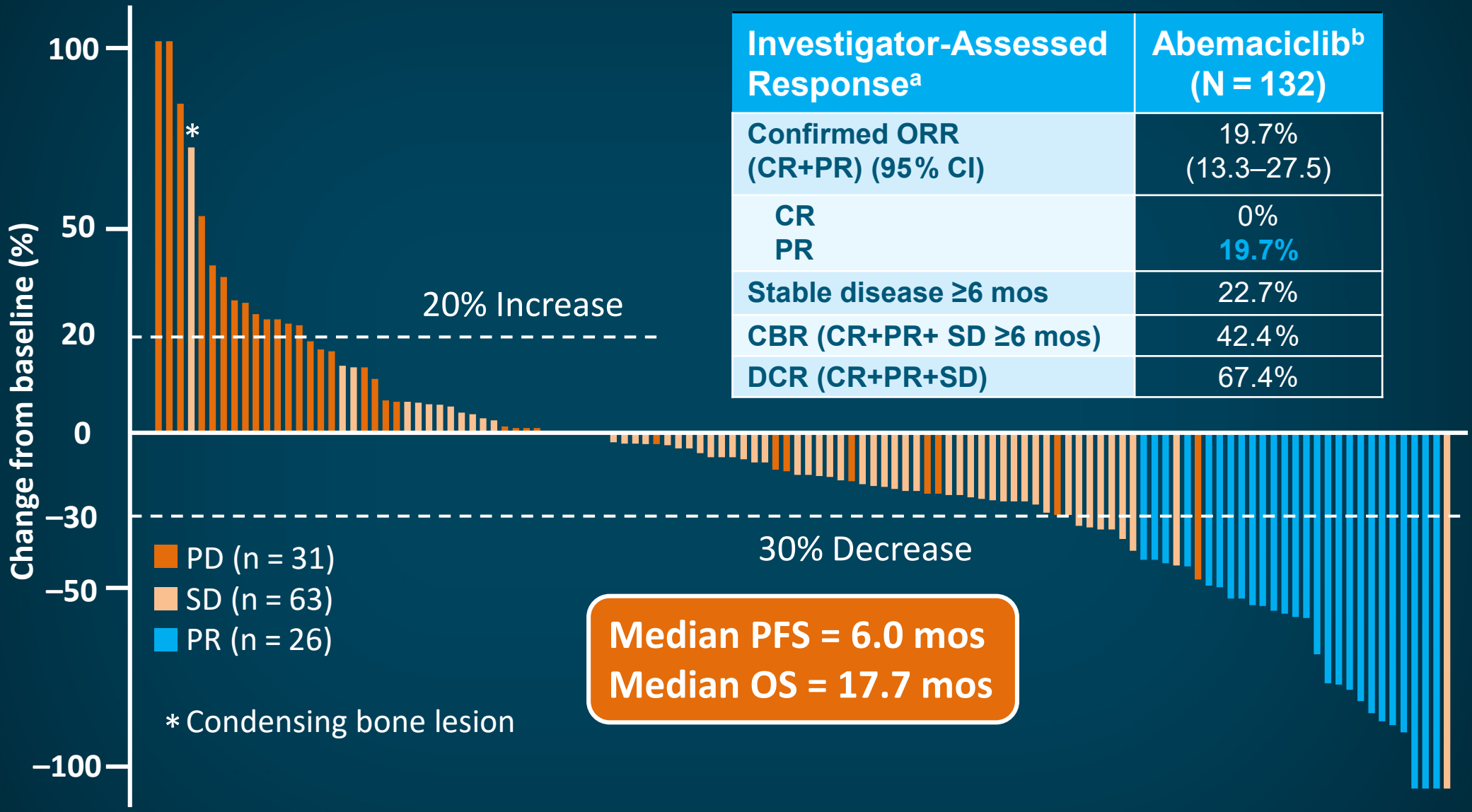
Secondary objectives

Duration of response, progression-free survival, overall survival, clinical benefit rate, safety

Statistical design

A sample size of 128 patients provides 82% power, assuming a true response rate of 25%, to exclude an ORR of ≤15% on the lower bound of the 95% CI at 12 months follow-up

MONARCH 1: Late-Line Abemaciclib ER+ MBC



Investigator-Assessed Response[a]	Abemaciclib[b] (N = 132)
Confirmed ORR (CR+PR) (95% CI)	19.7% (13.3–27.5)
CR	0%
PR	19.7%
Stable disease ≥6 mos	22.7%
CBR (CR+PR+ SD ≥6 mos)	42.4%
DCR (CR+PR+SD)	67.4%

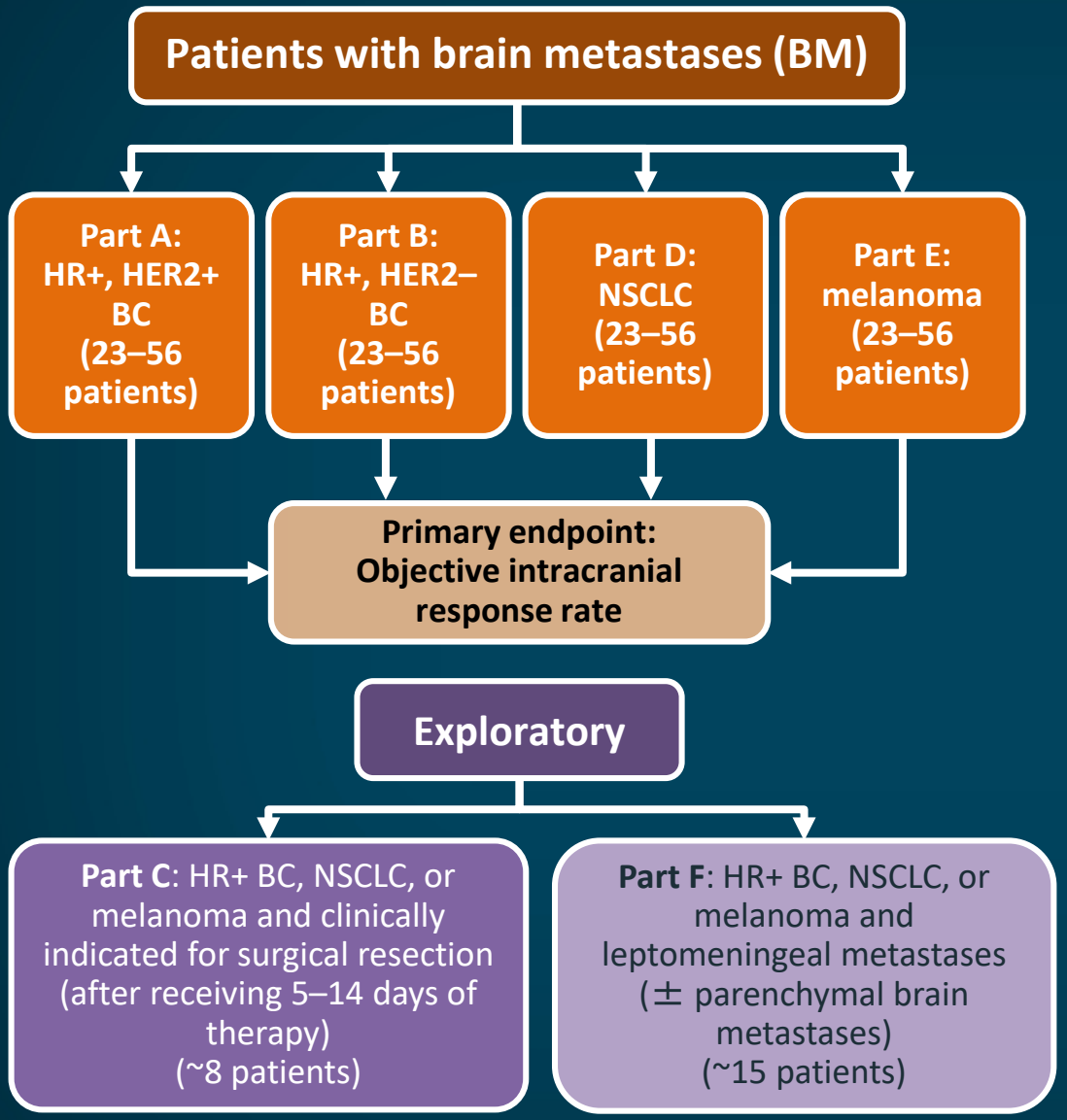
Median PFS = 6.0 mos
Median OS = 17.7 mos

[a]Assessments based on independent review were comparable. [b]200 mg monotherapy dose.

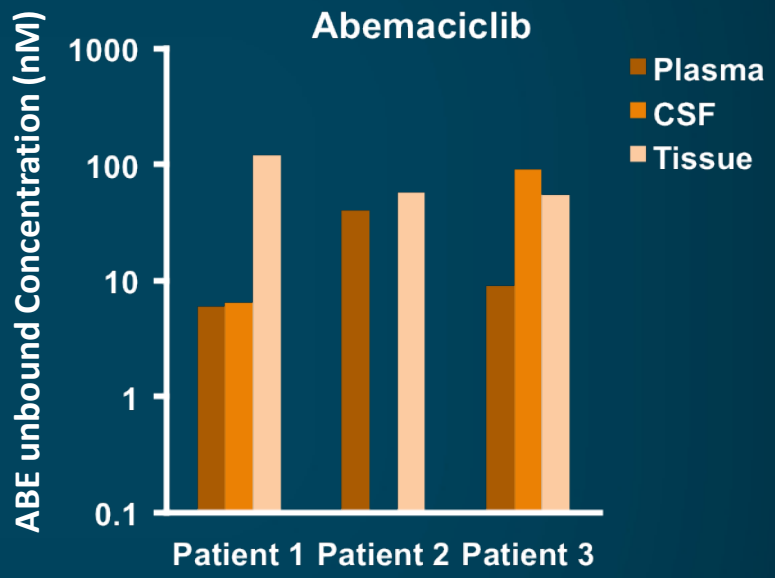
CR = complete response; PR = partial response; DCR = disease control rate; SD = stable disease.

Dickler MN et al. *Clin Cancer Res.* 2017;23:5218-5224.

Abemaciclib for Brain Metastases*



Plasma, CSF, and resected tumor tissue unbound concentrations of ABE



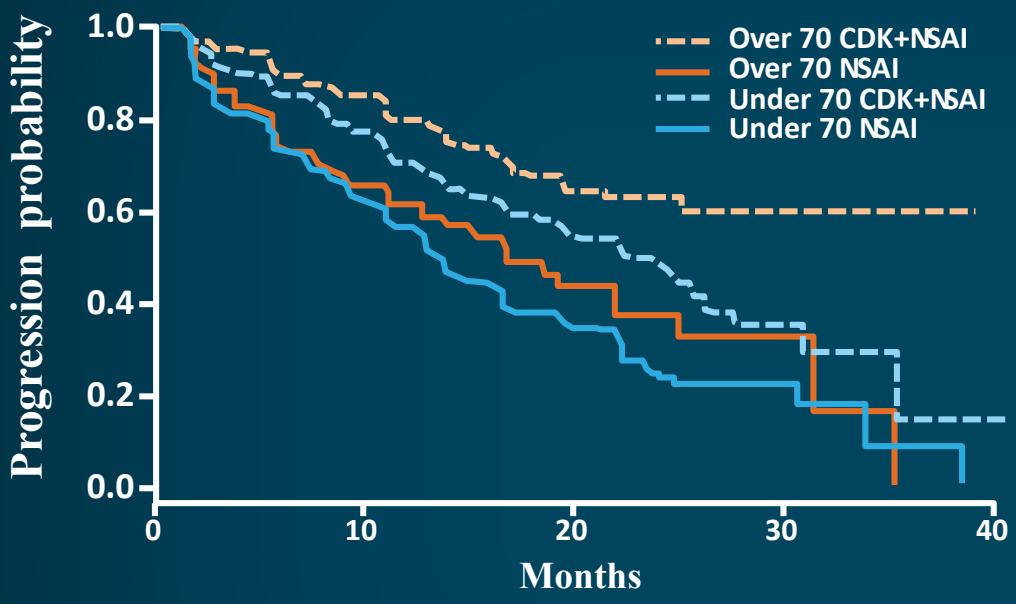
8.7% ORR; 17% CBR
Heavily-pretreated BM metastatic BC

NSCLC = non-small-cell lung cancer; CSF = cerebrospinal fluid. * Abemaciclib is not FDA-approved for this indication.

NCI02308020. Sahebjam S et al. *J Clin Oncol*. 2016;34(suppl): abstract 526. Tolaney SM et al. *J Clin Oncol.* 2017;35(suppl): abstract 1019.

US FDA Pooled Analysis of Outcomes of Older Women with HR+ MBC Treated with CDK4/6 Inhibitor as Initial Endocrine-Based Therapy

Efficacy of CDK4/6 Inhibitors in patients aged >70



	Median PFS (95% CI)
Age ≥70 CDK4/6 (n = 280)	**NR** (25.1 mos–NR)
Age <70 CDK4/6 (n = 826)	**23.75 mos** (21.9–25.4)
Age ≥70 AI only	**16.8 months** (13.7–21.9)
Age <70 AI only	**13.8 months** (12.9–14.7)

HR = 0.54 (95% CI, 0.47–0.62)

- Older patients with BC benefit from treatment with CDK4/6 inhibitors as initial endocrine-based therapy for HR+, HER2-negative MBC.
- Severity of AEs and rates of dose modifications and interruptions were higher in women aged ≥65, ≥70.
- Rates of selected adverse events similar across pooled trials

No treatment difference across age subgroups. Similar results with alternate age cut offs (aged >65, >75, etc.)

Singh H et al. SABCS 2017: abstract GS5-06.

Summary of 1st and 2nd line CDK4/6i Trials

Table 1. Select Randomized Clinical Studies of Endocrine Therapy Plus CDK4/6-Directed Therapy in Estrogen Receptor–Positive Metastatic Breast Cancer

Study	Regimen	Phase	No.	PFS, Endocrine Alone (months)	PFS, + CDK 4/6 Inhibitor (months)	Hazard Ratio (95% CI)
First line						
PALOMA-1	Letrozole with or without palbociclib	II	165	10.2	20.2	0.488 (0.319 to 0.748)
PALOMA-2	Letrozole with or without palbociclib	III	666	14.5	24.8	0.58 (0.46 to 0.72)
MONALEESA-2	Letrozole with or without ribociclib	III	668	14.7	25.3	0.56 (0.43 to 0.72)
MONARCH-3	NSAI with or without abemaciclib	III	493		NCT 21*	
Second line						
PALOMA-3	Fulvestrant with or without palbociclib	III	521	4.6	9.5	0.46 (0.36 to 0.59)
MONARCH-2	Fulvestrant with or without abemaciclib	III	669	9.3	16.4	0.553 (0.449 to 0.681)
MONALEESA-3	Fulvestrant with or without ribociclib	III	725		NCT02422615	

Abbreviations: CDK4/6, cyclin-dependent kinase 4/6; PFS, progression-free survival; NSAI, nonsteroidal aromatase inhibitor.
*Interim analysis reportedly met primary end point of improved PFS in the combination arm.[8]

Wander S, Mayer EL, Burstein HJ. J Clin Oncol 2017

SAFETY PROFILE

Side effects of CDK4/6 inhibitors

Table 2. Dosing and Toxicity for Cyclin-Dependent Kinase 4/6 Inhibitors

	Palbociclib (125 mg per day [3 weeks on, 1 week off])		Ribociclib (600 mg per day [3 weeks on, 1 week off])		Abemaciclib (200 mg twice per day [continuous])	
Common Adverse Event*	All Grades	Grade 3 and 4	All Grades	Grade 3 and 4	All Grades	Grade 3 and 4
Neutropenia	74-81	54-67	74	59	46	27
Thrombocytopenia	16-22	2-3	NR	NR	16	3
Fatigue	37-40	2-4	37	2	40	3
Diarrhea	21-26	1-4	35	1	86	13
Nausea	25-35	0-2	52	2	45	3
QTc prolongation	NR	NR	3	NR	NR	NR

NOTE. Data are given as percent.
Abbreviation: NR, not reported; QTc, corrected QT interval.
*Common adverse events in phase III trials in the metastatic setting.

Wander S, Mayer EL, Burstein HJ. J Clin Oncol 2017

Clinical Summary of CDKi in HR+ MBC

- Consistent clinical benefit and significant PFS improvements regardless of:
  - Age, menopausal state, prior endocrine therapy exposure, and endocrine therapy partner,
- Schedule of administration is convenient
- Treatment is associated with predictable, tolerable and manageable safety profile
  - Unique toxicities
    - Abemaciclib: diarrhea occurs early, dose related
    - Ribociclib: QTc prolongation; ECG q2 x 3
    - Neutropenia with low incidence of febrile neutropenia

Clinical Questions of CDKi in HR+ MBC

- When to best to integrate, first line, second line and later
- Can we select patients for CDK inhibition based in molecular or clinical characteristics
- Are these results in significant PFS would translate into significant improvement in overall survival
- What should we do do upon disease progression, switch hormonal agent and continue CDK inhibition or switch to hormonal therapy or chemotherapy alone?

Progression on CDK4/6 Inhibitors

- Per NCCN 2017 guidelines: If disease progression on CDK4/6 inhibitor + letrozole, there are no data to support an additional line of therapy with another CDK4/6 inhibitor regimen.
- Resistance mechanisms for CDK4/6
  - Rb mutation
  - Collateral pathways, eg, PI3K
  - Switch to cyclin E
  - Resistance to the endocrine therapy, eg, ESR1 or HER2 mutation
- Clinical trial approaches to overcoming resistance
  - CDKi-free period then rechallenge
  - Add additional agents (PI3K, mTOR inhibitors)
  - Switch endocrine therapies

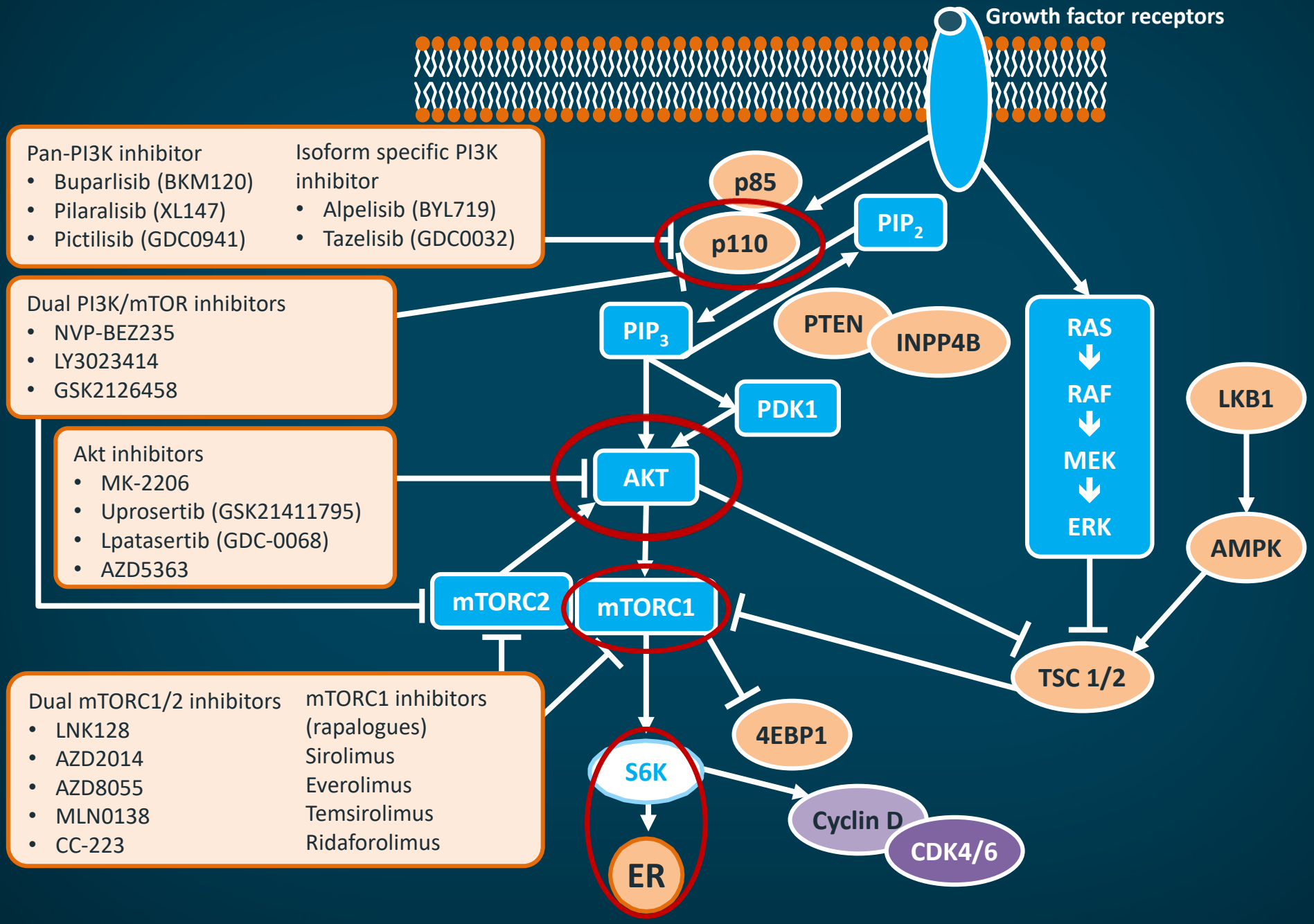
NCCN Clinical Practice Guidelines in Oncology. Breast Cancer V3. 2017. December 15, 2017. Turner NC,et al. *Lancet.* 2017;389:2403–2414.

Approaches to Overcoming Resistance to Endocrine Therapy

- **Alterations of downstream signaling pathways such as PI3K, (PI3K inhibitors)**

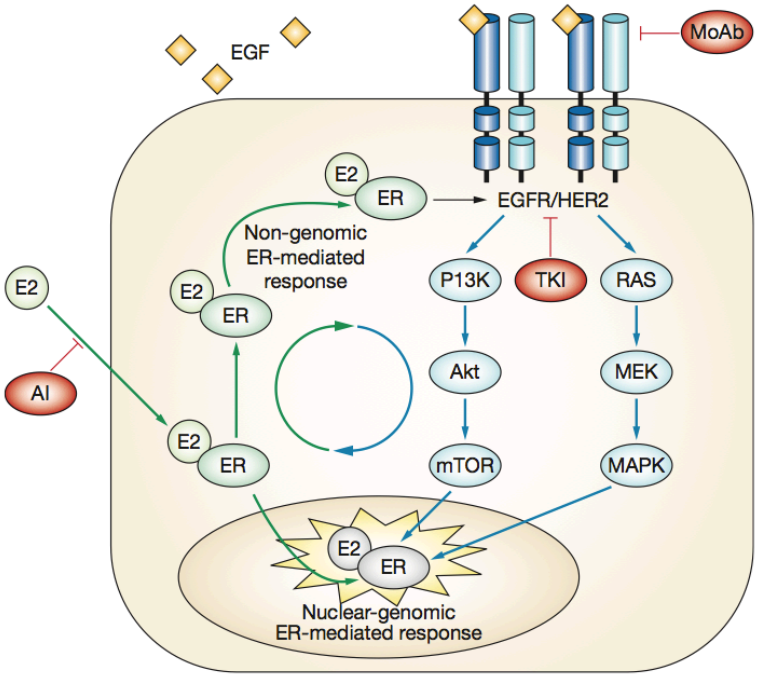
- Alterations of the cell cycle machinery (CDK inhibitors)

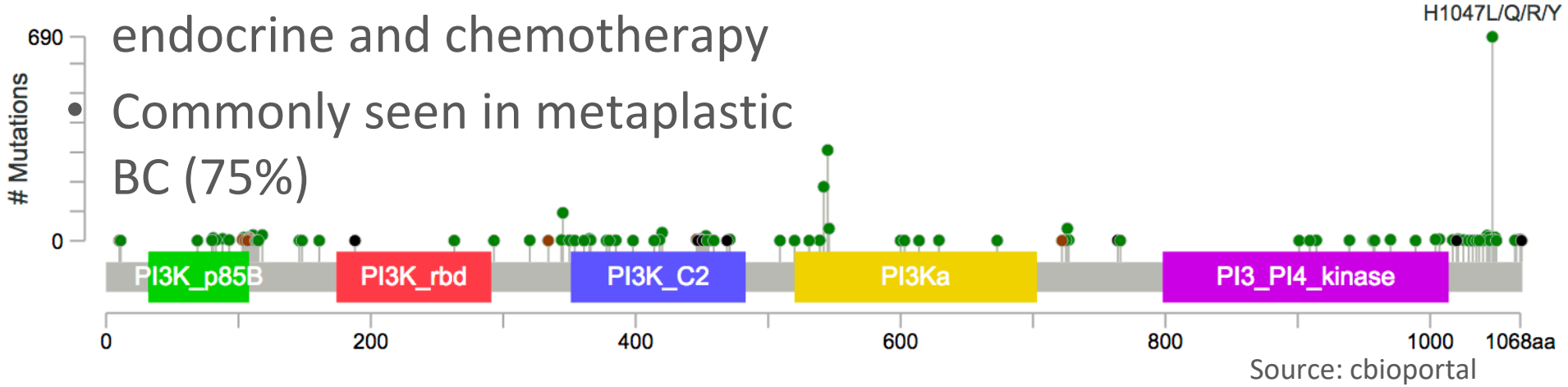
PI3 Kinase/mTOR Signaling



PIK3CA

- PI3K/mTOR/Akt pathway involved in tumor growth and survival
- PIK3CA most common oncogenic mutation in BC
- Mutations in 30-35% of HR positive BC
- Implicated in resistance to endocrine and chemotherapy
- Commonly seen in metaplastic BC (75%)





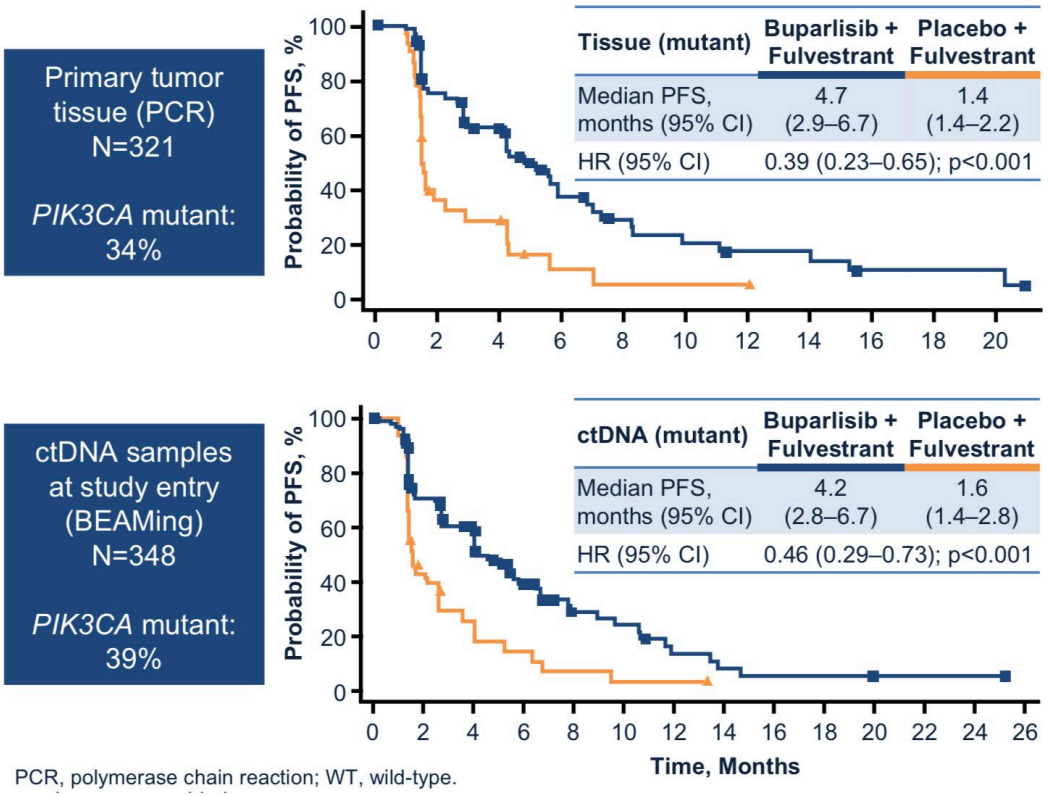
Source: cbioportal

PIK3CA

Buparlisib plus Fulvestrant vs. Fulvestrant

BELLE-3

- Phase-3 for ER +ve MBC
- Progressed on endocrine therapy or mTOR inhibitor (2:1)
- PFS improvement in PIK3CA mut
- LFT alteration, hyperglycemia, HTN with Buparlisib

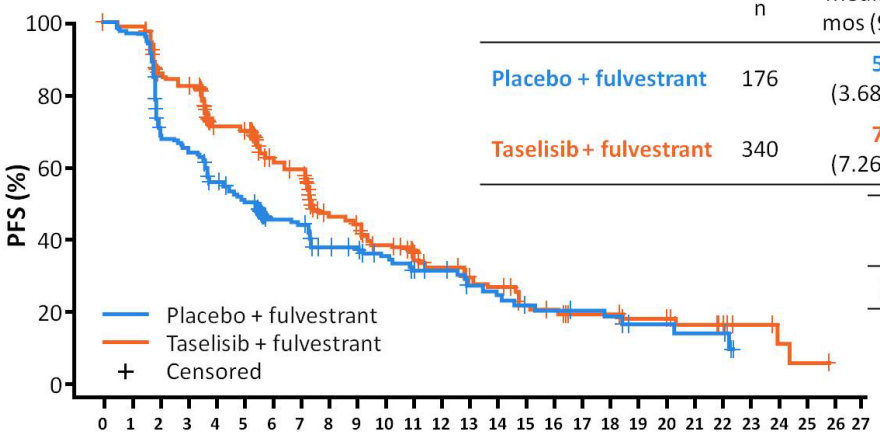


PCR, polymerase chain reaction; WT, wild-type.

Di Leo, Lancet Onc 2018

PIK3CA

Taselisib plus Fulvestrant vs. Fulvestrant



	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%

SANDPIPER

- ER +ve MBC
- Post menopausal
- *PIK3CA* mutation positive
- Recurrence on AI
- No Prior everolimus

- Expected AE – GI Toxicity and hyperglycemia
- Issues with tolerability, frequent interruptions

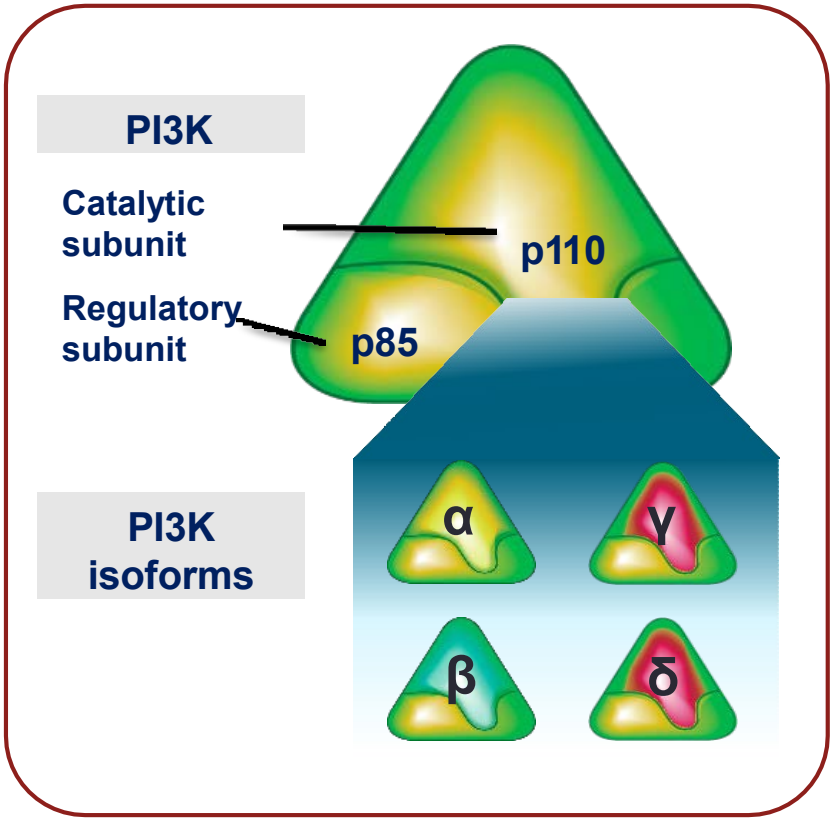
Baselga ASCO 2018

PIK3CA mutations and alpelisib

- PI3K enzyme has four isoforms (α, β, δ, γ)[1]
- Previously investigated PI3K inhibitors targeted multiple isoforms and their associated toxicities precluded further development and prompted the need for selective PI3K inhibitors[2-4]
- Alpelisib (BYL719) is an inhibitor of the PI3K α-isoform[1]

– Alpelisib inhibits the α-isoform of PI3K 50 times more potently than other PI3K isoforms (β, δ, γ)[5]

- Alpelisib has demonstrated antitumor activity in preclinical models harboring *PIK3CA* alterations[1]



PI3K, phosphatidylinositol-3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

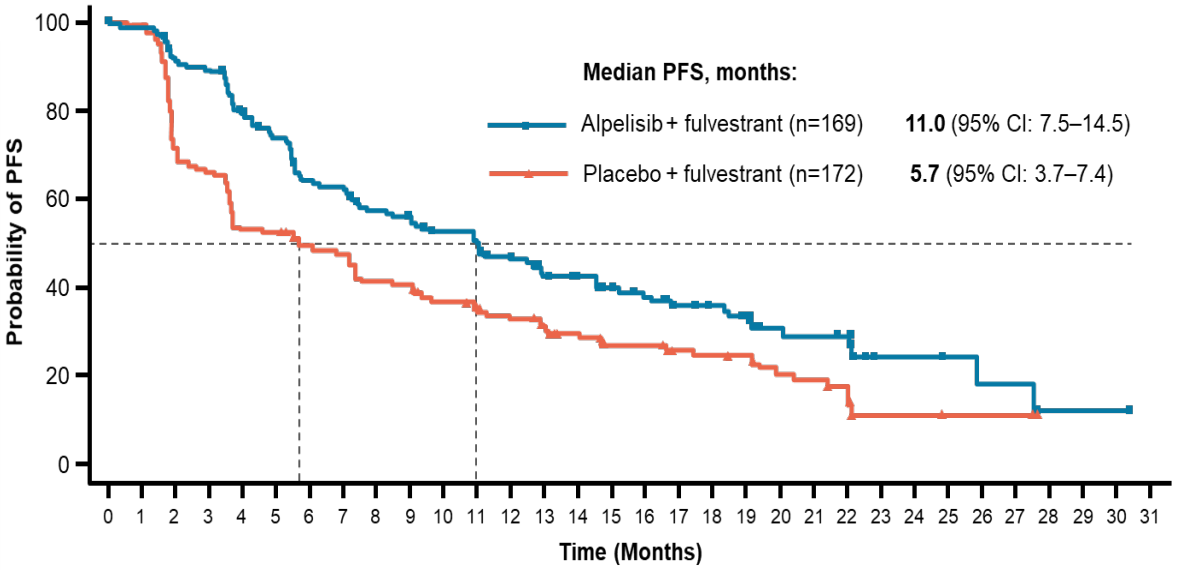
1. Fritsch C, et al. *Mol Cancer Ther* 2014;13:1117–1129; 2. Baselga J, et al. *J Clin Oncol* 2018;36 (Suppl): LBA 1006; 3. Di Leo A, et al. *Lancet Oncol* 2018;19:87–100; 4. Baselga J, et al. *Lancet Oncol* 2017;18:904–916; 5. Furet P, et al. *Bioorg Med Chem Lett* 2013;23(13):3741-8.

PIK3CA

Alpelisib plus Fulvestrant vs. Fulvestrant

SOLAR

- ER +ve MBC, Recurrence on prior AI
- Alpha specific isoform inhibitor
- *PIK3CA* mutation +ve
- G3 hyperglycemia 33%, 10% rash
- No difference in non-mutants
- Activity in both exon 9 and exon 20 mutations
- ORR 36%



Andre ESMO 2018

Genomics to Perform Precise Medicine in Patient with ER+ MBC

ESR1

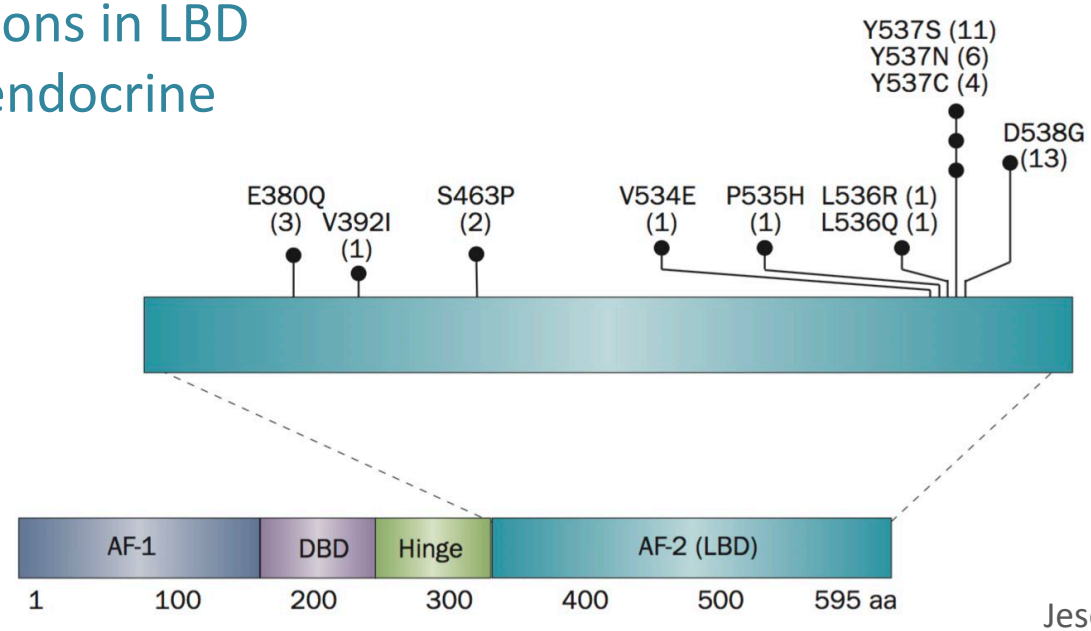
Activating *ESR1* mutations in hormone-resistant metastatic breast cancer

Dan R Robinson[1,2,12], Yi-Mi Wu[1,2,12], Pankaj Vats[1,2], Fengyun Su[1,2], Robert J Lonigro[1,3], Xuhong Cao[1,4], Shanker Kalyana-Sundaram[1,2], Rui Wang[1,2], Yu Ning[1,2], Lynda Hodges[1], Amy Gursky[1,2], Javed Siddiqui[1,2], Scott A Tomlins[1,2], Sameek Roychowdhury[5], Kenneth J Pienta[6], Scott Y Kim[7], J Scott Roberts[8], James M Rae[3,9], Catherine H Van Poznak[9], Daniel F Hayes[9], Rashmi Chugh[9], Lakshmi P Kunju[1,2], Moshe Talpaz[9], Anne F Schott[9] & Arul M Chinnaiyan[1–4,10,11]

ESR1 ligand-binding domain mutations in hormone-resistant breast cancer

Weiyi Toy[1], Yang Shen[2], Helen Won[1], Bradley Green[3], Rita A Sakr[4], Marie Will[5], Zhiqiang Li[1], Kinisha Gala[1], Sean Fanning[3], Tari A King[4], Clifford Hudis[5,6], David Chen[7], Tetiana Taran[7], Gabriel Hortobagyi[8], Geoffrey Greene[3], Michael Berger[1,9], José Baselga[1,5] & Sarat Chandarlapaty[1,5,6]

Acquired *ESR1* mutations in LBD mediates secondary endocrine resistance

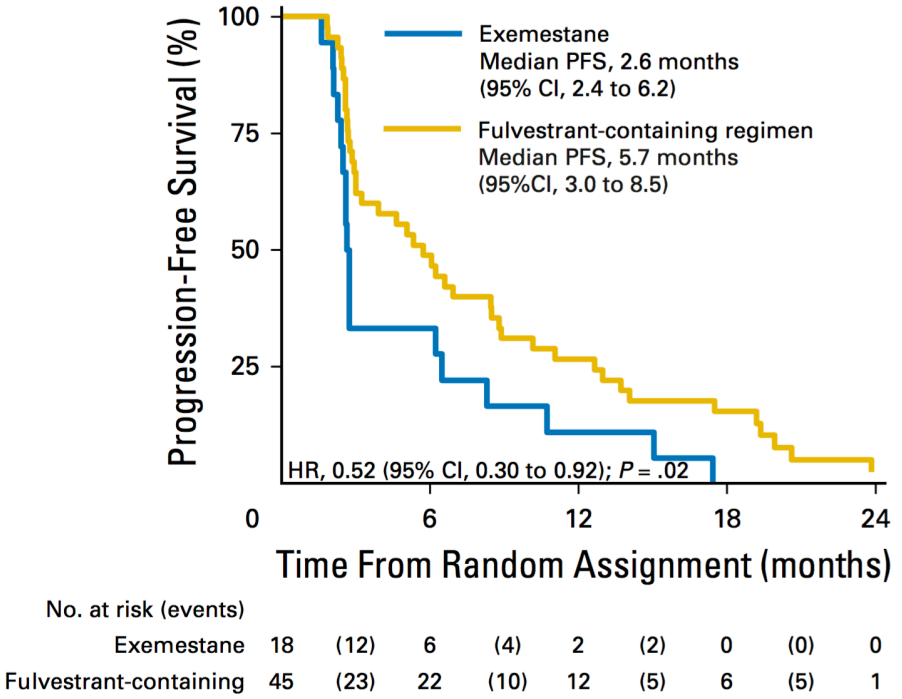


Jeselsohn et al. 2015

ESR1

- Uncommon in primary tumors
- Currently, the most effective therapy for *ESR1* mutations is unknown
- Fulvestrant might have activity on select *ESR1* variants
- Novel SERDs are being developed

Study	Frequency
FERGI	40%
SOFEA	40%
BOLERO-2	30%
Clatot	31%
PALOMA-3	25%



Chandarlapaty et al.2016, Clatot et al. 2016, Johnston et al. 2013, Krop et al. 2016, Turner et al. 2015

Translational Studies in Search of Biomarkers

- TAMRAD:
  - Patients with high p4EBP1, low 4EBP1, low liver kinase B1, low pAkt, and low PI3K were most likely to have improved TTP with everolimus.
  - Everolimus efficacy was positively associated with late effectors of mTORC1 activation, AKT-independent mTORC1 activation and negatively associated with PI3K/AKT/mTOR pathway.
- BOLERO-2:
  - Quantitative differences in everolimus benefit were observed between patient subgroups defined by the exon-specific mutations in PIK3CA (exon 20 v 9) or by different degrees of chromosomal instability in the tumor tissues.

Treilleux I, et al. *Ann Oncol* 26(1):120-125, 2015; Hortobagyi GN, et al., J Clin Oncol 34(5):419-426, 2016.

Efficacy of cdk 4/6-inhibitors Plus Endocrine Therapy by Baseline Tumor Markers

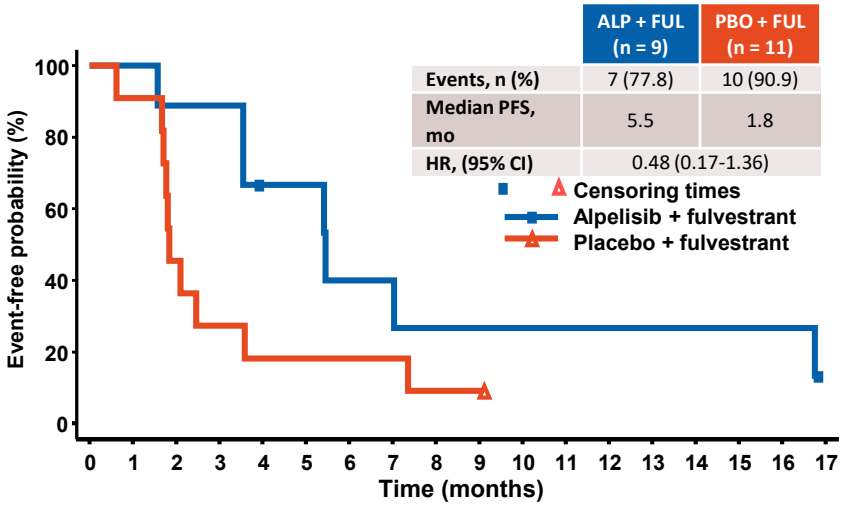
- The Benefit of ribociclib plus letrozole is not altered by
  - Total Rb, Ki67 and p16 expression (IHC);
  - mRNA expression of *CCND1*, *CDKN2A*, and *ESR1*;
  - Presence of *PIK3CA* mutations or tp53 alterations (ctDNA sequencing)
- Quantitative reductions in treatment benefit were observed with
  - RTK gene, CDH1, FGFR1/ZNF703 (8p11.23) alterations (circulating tumor DNA)
  - Sample numbers were limited; these observations need validation

Andre F, et al. AACR 2017 (CT045); Turner N, et al. ASCO 2016; Hortobagyi GN, et al. SABCS 2017. PD4-06

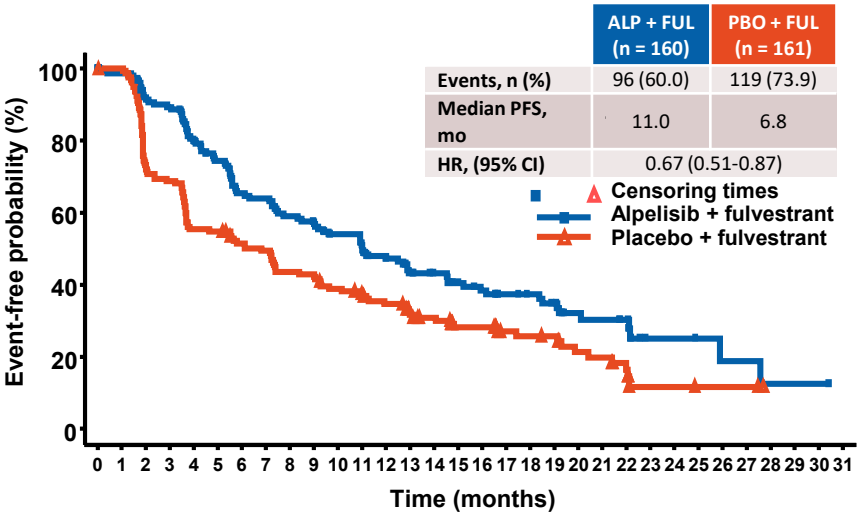
PIK3CA

Alpelisib plus Fulvestrant vs. Fulvestrant

With Prior CDK4/6 inhibitor therapy



Without Prior CDK4/6 inhibitor therapy



Overall Survival Not Mature

Andre ESMO 2018

Take home points in HT in ER+ HER-2- MBC

- Endocrine therapy is the cornesrtone of the treatment of HR+ MBC.

- Combined AI and SERD treatment might be more effective than an AI alone for ET-naïve patients with ER+ MBC no candidate to CDK 4/6 inhibitors

- M-THOR and PI3K inhibitors plus HT provide superior clinical benefit and PFS than HT alone in hormone-resistant ER+ MBC – clinical benefit when used in combination with endocrine therapy.
  - Challenges: Toxicities and patient selection

- CDK inhibitors plus HT is the standard of care in first or second line setting. All agents with nearly identical activity but have different side effect profiles. Optimal use" remains unclear and survival data is still evolving

- Resistance to endocrine therapy is a challenge. Mutations of the PI3K pathway are frequent in breast cancer. Aberrations in PI3K – Common mechanism of endocrine resistance.

Hormonal Therapy for Advanced Breast Cancer: Milestones

1896 — Oophorectomy and response to advanced disease

1951 — Estrogen drives breast cancer

1977 — Estrogen receptor (ER) identified; Tamoxifen approved

1990's — Immuno-histochemistry developed for ER and PR analysis

1999 — First selective aromatase inhibitor (AI) approved for ABC

2002 — ER downregulator approved; AI approved as adjuvant therapy

2010 — AntiHER2 + AI approved for ER/HER2+ ABC

2012 — mTOR inhibitor + AI approved

2015 — CDK 4/6 Inhibitor + AI approved

Love RR, Philips J. *J Natl Cancer Inst*. 2002;94:1433-1434; Allred DC, et al. *Mod Pathol.* 1998;11:155-168; Bross PF, et al. *Oncologist.* 2002;2:477-480; Cohen MH, et al. *Oncologist.* 2001;6:4-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