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Optimizing Endocrine Therapy in Advanced Breast Cancer

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Disclosures

- None

Overview

- Advanced breast cancer (ABC): 60-75% ER positive
- Higher ER pos with age
- ER + ABC cell proliferation driven by ER mediated gene transcription, a "SURVIVAL" pathway
- Endocrine therapy (ET) represents therapeutic backbone
- Eventual ET resistance limits therapeutic options

Outline

- ET monotherapy
- ET combination therapy: CDK 4/6, mTORi, PI3Ki, HDACi

Treatment Considerations

- Minimize toxicity
- Maintaining QOL
- Urgency for response
- Duration of or prior exposure to endocrine therapy (ET)
- Duration of prior DFI
- Sites of disease
- Comorbidities
- Patient access, cost of drugs
- ET resistance

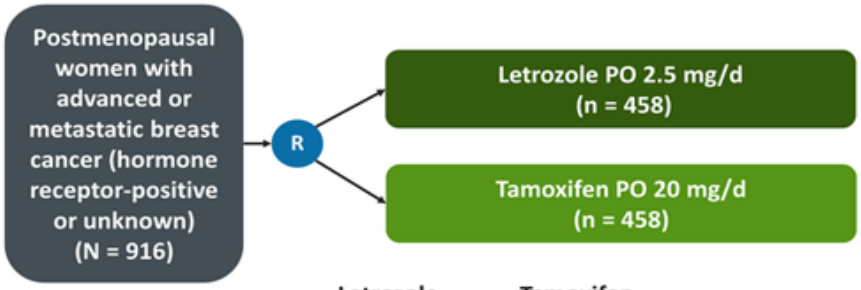
ET Agents

Agents	Mechanism	Indication	AEs
LHRH antagonists: Goserelin Leuprolide	Blocks ovarian function and production of estrogen	Palliative treatment of ABC in pre- and perimenopausal women	DUB, hot flushes, HA, sweating, acne, emotional lability, depression decreased libido, tumor flare
Selective ER Modulators: Tamoxifen Toremifene	Competitive inhibitors of estrogen, bind directly to ER on BC cells	Treatment for ER pos ABC women, men	Hot flashes, night sweats, vaginal dryness/discharge, bleeding, endometrial cancer, DVT
Aromatase Inhibitors Nonsteroidal: Anastrozole Letrozole Steroidal: Exemestane	Decrease amount of estrogen in post-menopausal women by blocking conversion of androgens to estrogen; steroidal AI substrates bind irreversibly	1st line treatment for ER positive ABC	Musculoskeletal symptoms, hot flashes, vaginal dryness, bone loss, edema, headache, dizziness, hyperlipidemia, increased seating, increased appetite (exemestane)
Selective ER Degrader: Fulvestrant	Binds competitively to ER, inhibits ER dimerization and translocation to nucleus; accelerates ER degradation	ER pos ABC with PD following antiestrogen therapy	Injection site pain, nausea, bone pain, arthralgia, headache, fatigue, hot flashes, anorexia, asthenia, increased LFT's

ET Monotherapy in ABC

Letrozole vs Tamoxifen in Advanced Breast Cancer

- Randomized phase 3 trial



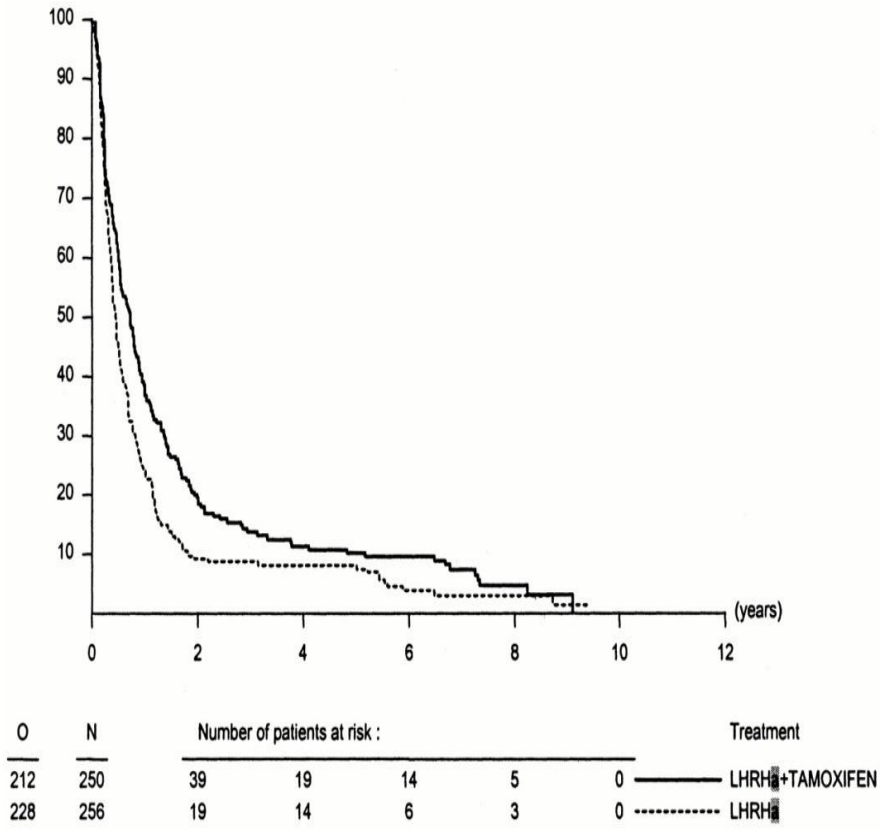
	Letrozole (n = 453)	Tamoxifen (n = 454)	*P* Value
Median TTP, mo	9.4	6.0	<.0001
Median TTF, mo	9.0	5.7	<.0001
Median TTC, mo	16	9	.005

Mourisdon H, et al. *J Clin Oncol.* 2003;21:2101-2109.

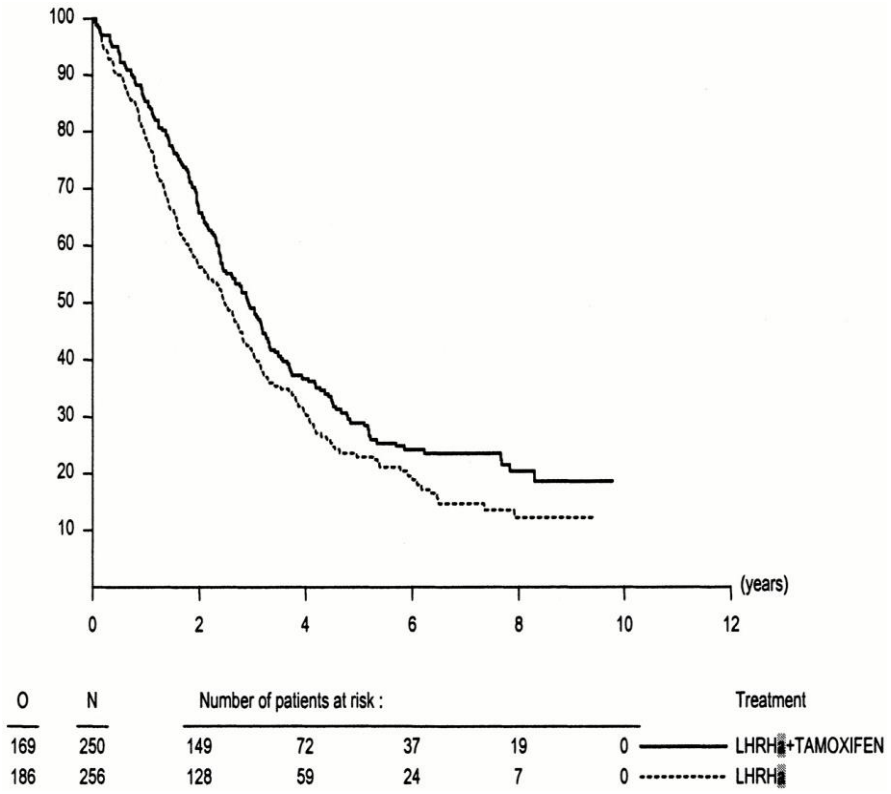
ET Monotherapy Trials: AI Vs Tam in ABC

	EXE 25 mg vs. Tam 20 mg		ANA 1 mg vs. Tam 20 mg		LET 2.5 mg vs. Tam 20 mg	
Patients, n	182	198	511	510	458	458
CR +PR	**44%**	29%	29%	27%	**30**	20
CR+PR+SD			**57%**	**52%**	**49**	38
Med. TTP	**8.9 mo**	5.2 mo	**259 d**	**212 d**	**41 wk**	26 wk

ET: Tam Plus Ovarian Suppression



PFS



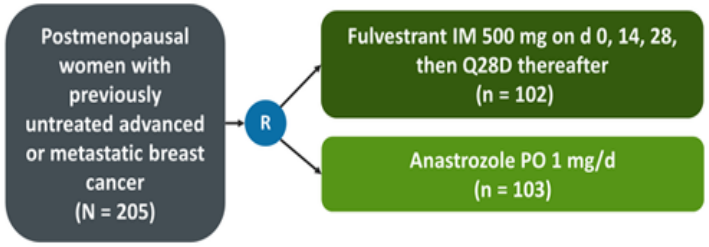
OS

Klijin, J Clin Oncol 19:343-353. 2001

FIRST Trial: SERD vs. AI

Fulvestrant vs Anastrozole in Advanced Breast Cancer: FIRST Trial

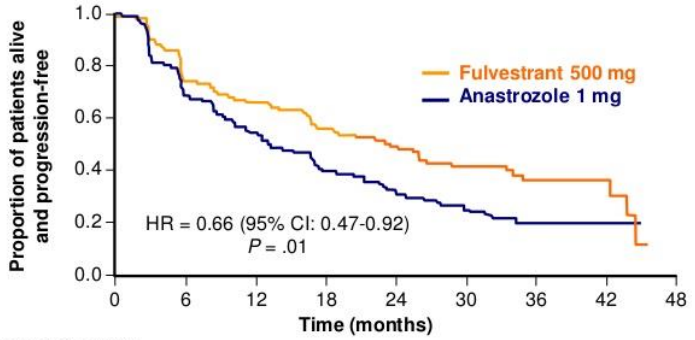
- Open-label, randomized phase 2 trial



	Fulvestrant	Anastrozole	HR (95% CI)	*P* Value
Median TTP, mo	23.4	13.1	0.66 (0.47, 0.92)	.01
Median OS, mo	54.1	48.4	0.70 (0.50, 0.98)	.04

Ellis MJ, et al. *J Clin Oncol.* 2015;33:3781-3787.

FIRST: Fulvestrant 500 mg *vs.* Anastrozole as First-Line



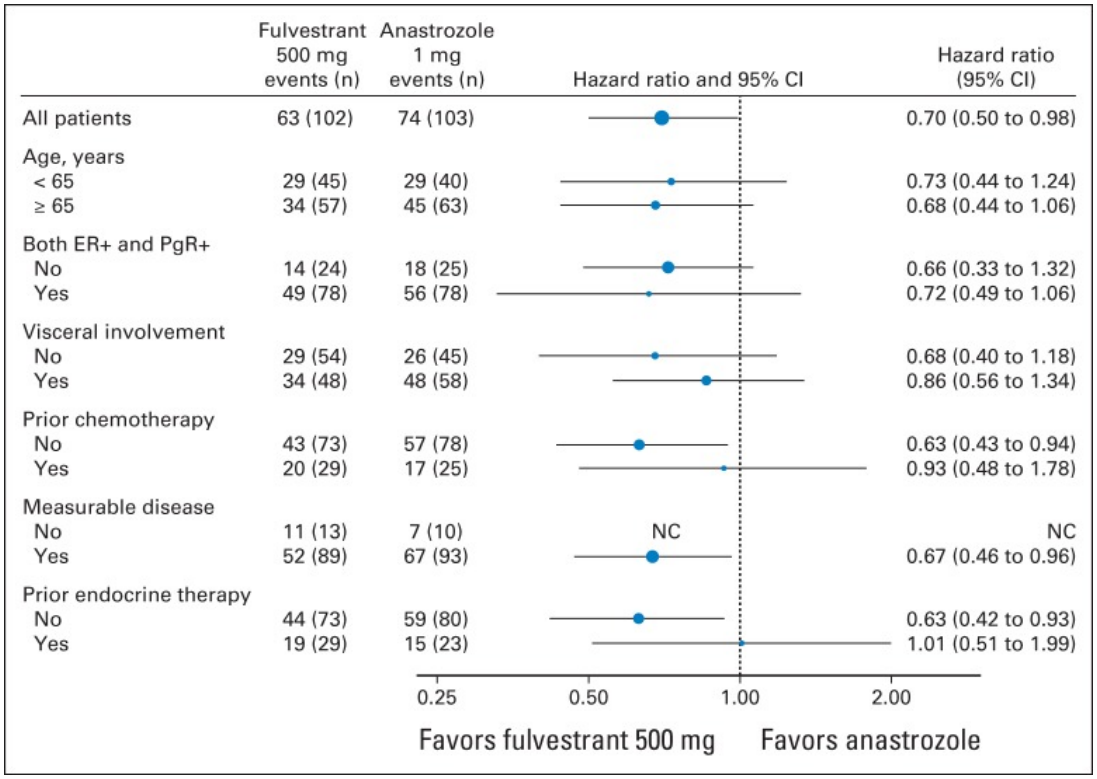
Number of patients at risk:

Fulvestrant 500 mg	102	74	65	52	45	34	20	6	0
Anastrozole 1 mg	103	69	55	39	30	21	8	2	0

CI = confidence interval; HR = hazard ratio; TTP = time to progression

Robertson JF, et al. Cancer Res. 2010;70: Abstract S1-3.

FIRST Trial: Subgroup Analysis



Ellis MJ JCO 2015

SERD vs. AI: FALCON

Fulvestrant vs Anastrozole in Advanced Breast Cancer: FALCON Trial

- Randomized, double-blind, phase 3 trial

Patients with hormone receptor-positive, HER2-, advanced BC w/no prior endocrine therapy (N = 462)

R

Fulvestrant IM 500 mg on d 0, 14, 28, then Q28D thereafter (n = 230)

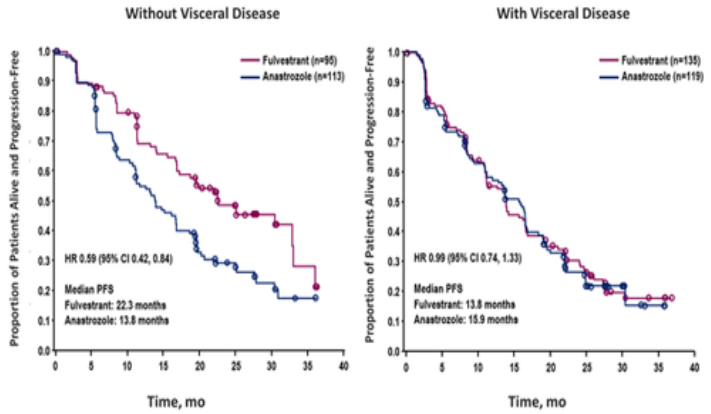
Anastrozole PO 1 mg/d (n = 232)

	Fulvestrant	Anastrozole	*P* Value
Median PFS, mo			
• Overall	16.6	13.8	.048
• Without visceral disease	22.3	13.8	
Common AEs, %			
• Arthralgia	16.7	10.3	
• Hot flushes	11.4	10.3	

Ellis MJ, et al. ESMO 2016. Abstract LBA14_PR.

FALCON Study

PFS in Patients With or Without Visceral Disease



Robertson J, et al. Lancet. 2016. In Press. With permission from Elsevier.

ET Resistance

- Resistance caused by:
  - Loss of ER expression and/or function
  - Loss of PR expression
  - Loss of ER dependence
  - ESR1 mutation
  - Constitutive PI3K activation
  - NF1 mutation

ESR1 Mutation

- Acquired mutation in gene encoding ER-α
- Most frequent mutations are activating and occur in ligand binding site
- <1% of treatment naïve primary tumors
- Acquired in up to 39% of patients who progress on Ais
- Associated with poor response to AI, shorter survival

ESR1 Mutation Affects ET Response

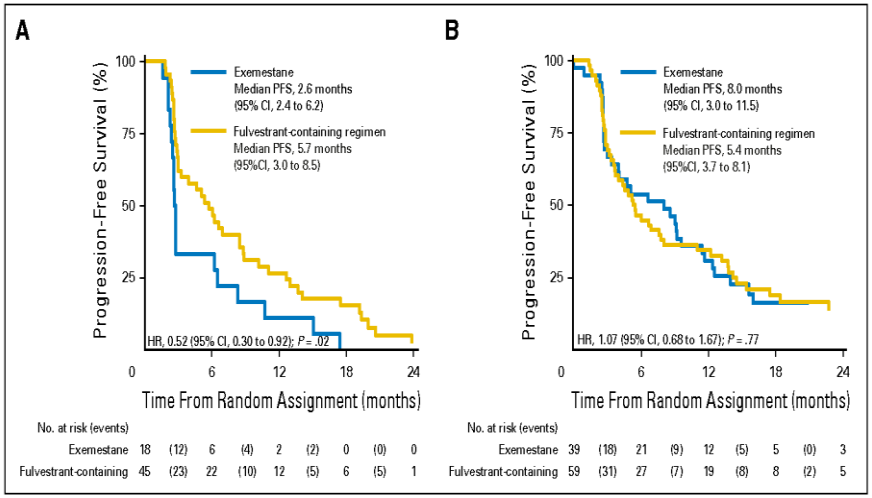


Fig 2. Progression-free survival (PFS) in SoFEA by *ESR1* mutation status. (A) PFS of patients with *ESR1* mutant cancers who received exemestane or a fulvestrant-containing regimen. (B) PFS of patients without detected *ESR1* mutation who received exemestane or a fulvestrant-containing regimen. HR, hazard ratio.

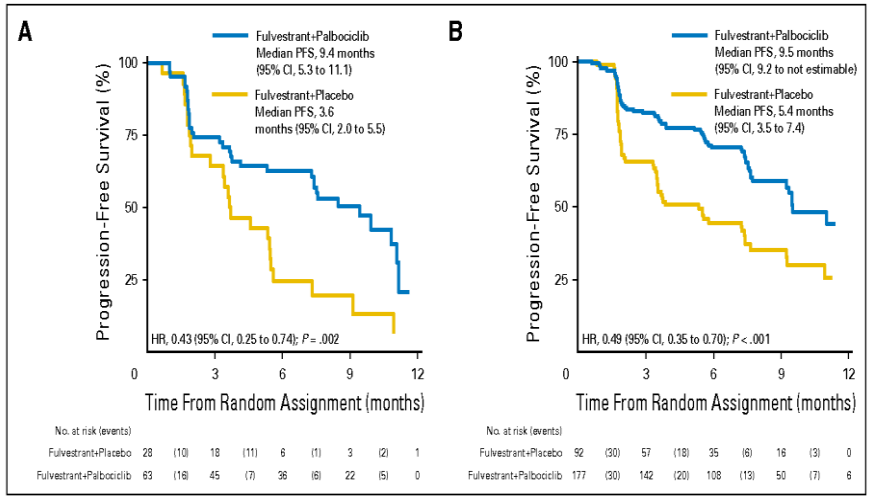


Fig 3. Progression-free survival (PFS) in PALOMA3 by *ESR1* mutation status. (A) PFS for patients with *ESR1* mutant cancers who received fulvestrant and placebo or fulvestrant and palbociclib. (B) PFS for patients without detected *ESR1* mutation who received fulvestrant and placebo or fulvestrant and palbociclib. HR, hazard

SoFEA Trial

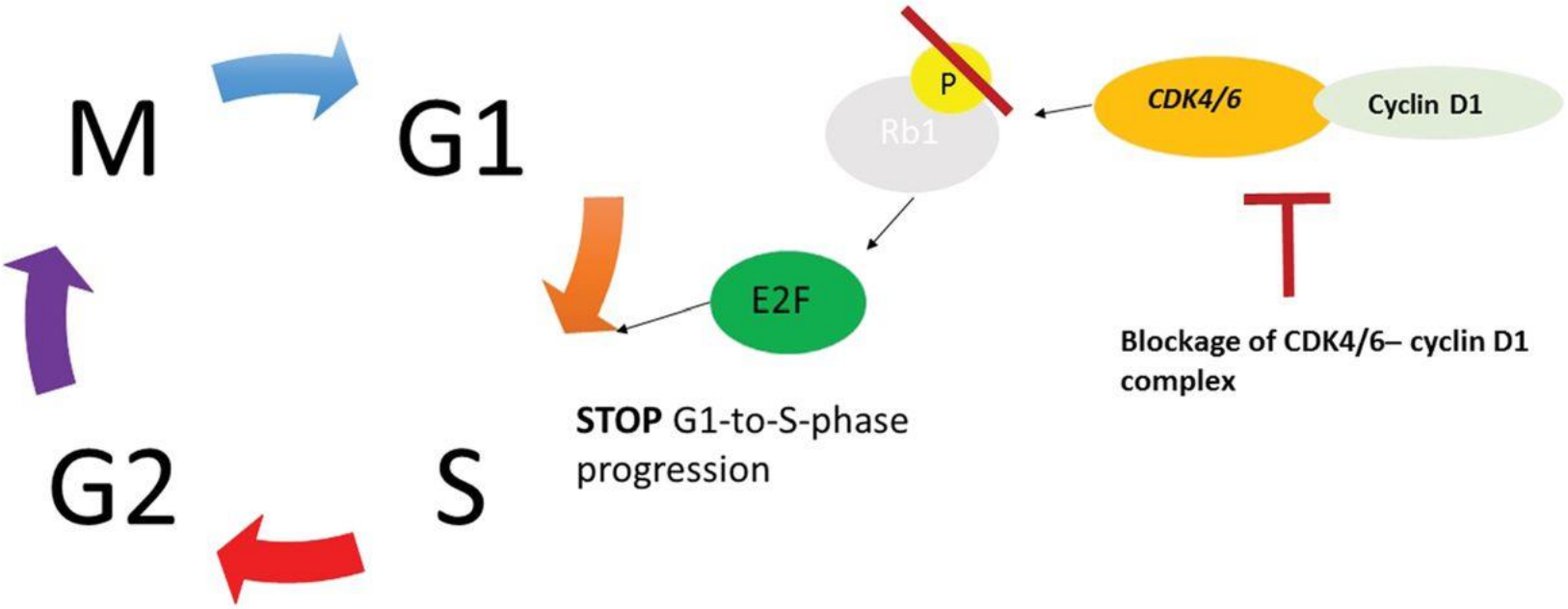
PALOMA-3

ET: Combination Therapy

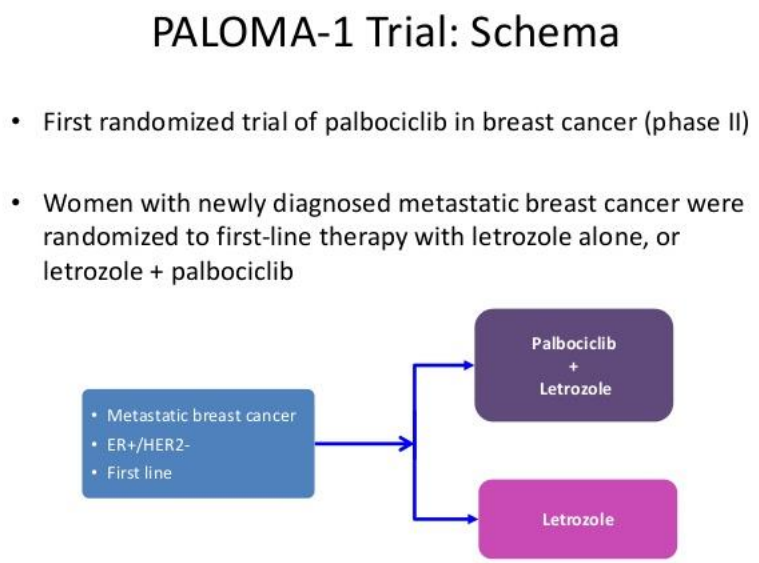
- ET plus CDK 4/6i
- ET plus mTORi
- ET plus novel agents

ET: Combination Therapy

Loss of cell cycle regulation leads to uncontrolled cellular proliferation

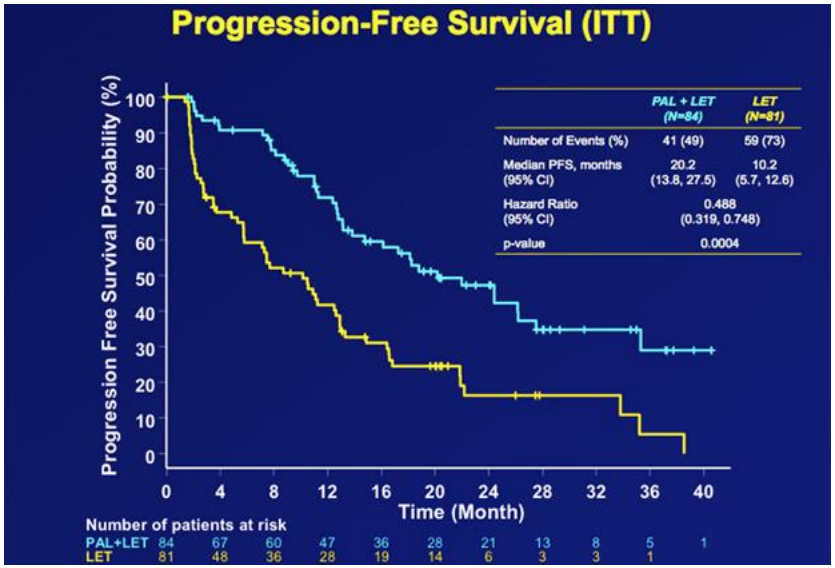


PALOMA-1



Randomized, phase II study, previously untreated postmenopausal woman with ER+ ABC

PALOMA-1



Randomized, phase II study, previously untreated postmenopausal woman with ER+ ABC

PALOMA-2

PALOMA-2
Palbociclib Plus Letrozole vs Letrozole Alone

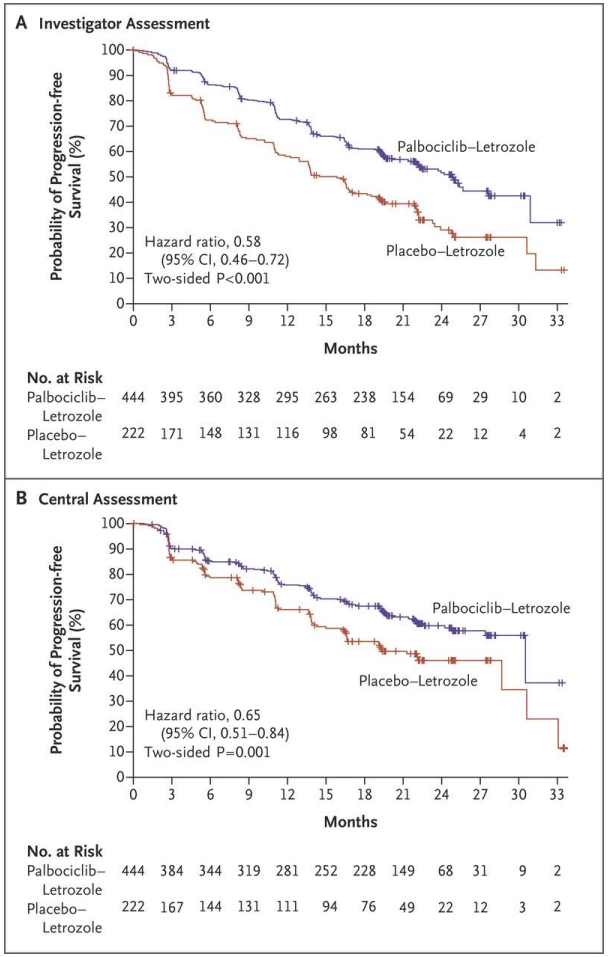
- Multicenter, international, double-blind, randomized, phase 3 study
- Postmenopausal women with ER+/HER2- advanced breast cancer, no prior treatment for advanced disease, no AI resistance (N = 666)
- Stratified by disease site, disease-free interval, prior neoadjuvant or adjuvant hormonal therapy
- Primary endpoint: PFS by investigator
- Secondary endpoints: OS, ORR, CBR, patient-reported outcomes and safety

Palbociclib 125 mg/d + letrozole 2.5 mg/d continuously (n = 444)

OR

Placebo + letrozole 2.5 mg/d (n = 222)

Finn RS, et al. *J Clin Oncol*. 2016;34(suppl). Abstract 507.



PALOMA-3

PALOMA-3
Palbociclib Plus Fulvestrant in Premenopausal/Perimenopausal mBC

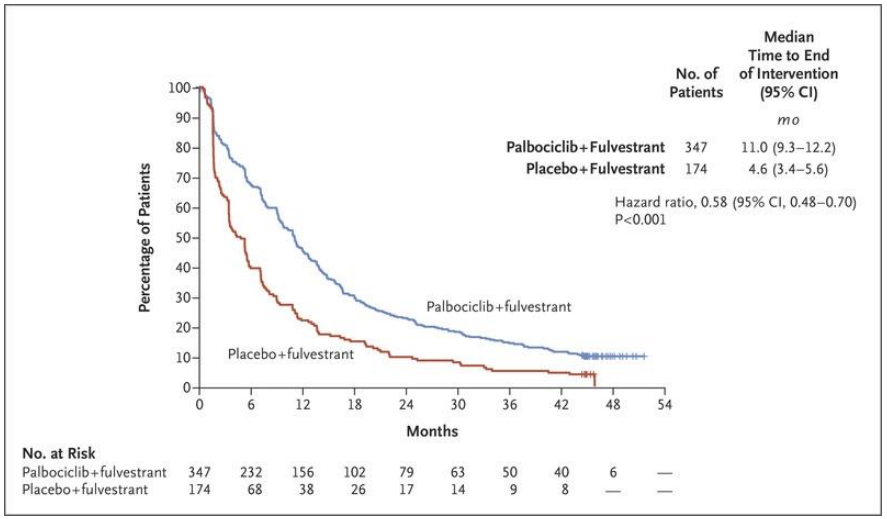
- Patients with hormone receptor-positive/HER2-negative mBC
- Premenopausal women received ovarian suppression starting 4 weeks or longer before randomization and throughout treatment with goserelin
- Primary objective: prolonged PFS for palbociclib plus fulvestrant vs placebo plus fulvestrant
- Secondary objectives: subgroup analyses of PFS, tumor control, CBR, ORR, safety/tolerability

Palbociclib (125 mg/d orally) for 3 wk followed by 1 wk off plus fulvestrant (500 mg) (n=347)

OR

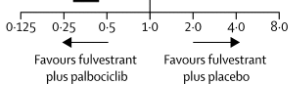
Placebo plus fulvestrant (n=174)

Cristofanilli M, et al. *Lancet*. 2016;17:425-439.

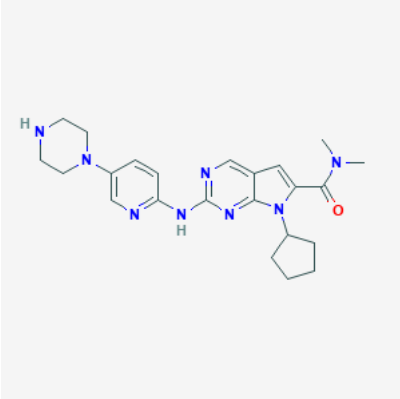


PALOMA-3

	Fulvestrant plus palbociclib (events [n]/ patients)	Fulvestrant plus placebo (events [n]/ patients)	Events (n)/ patients	Fulvestrant plus palbociclib median progression-free survival (95%CI)	Fulvestrant plus placebo median progression-free survival (95%CI)	Hazard ratio (95% CI)	$p_{interaction}$
Menopausal status at study entry							0·89
Premenopausal or perimenopausal	30/72	23/36	53/108	9·5 (7·4–NE)	5·6 (1·8–7·6)	0·50 (0·29–0·87)	
Postmenopausal	115/275	91/138	206/413	9·9 (8·5–11·0)	3·9 (3·5–5·5)	0·45 (0·34–0·59)	
Site of metastatic disease							0·82
Visceral	101/206	76/105	177/311	8·0 (7·5–9·5)	3·5 (2·0–5·3)	0·47 (0·34–0·63)	
Non-visceral	44/141	38/69	82/210	11·2 (9·9–NE)	5·6 (4·6–10·9)	0·43 (0·28–0·67)	
Number of disease sites							0·43
1	36/111	29/60	65/171	11·2 (9·9–NE)	9·3 (5·5–NE)	0·55 (0·34–0·90)	
2	40/95	36/51	76/146	11·0 (7·5–NE)	3·6 (1·9–5·6)	0·37 (0·24–0·59)	
≥3	69/139	49/62	118/201	7·6 (7·4–9·5)	3·4 (1·9–3·7)	0·40 (0·28–0·59)	
Disease-free interval							0·16
≤24 months	24/41	15/22	39/63	7·2 (2·5–9·2)	5·4 (1·8–9·3)	0·83 (0·43–1·59)	
>24 months	77/192	63/101	140/293	9·9 (9·3–11·2)	5·5 (3·5–7·3)	0·48 (0·35–0·68)	
Previous lines of endocrine therapy							0·75
1	63/160	58/91	121/251	9·5 (7·6–NE)	4·6 (3·4–5·6)	0·42 (0·29–0·60)	
2	61/140	44/61	105/201	9·9 (7·5–13·9)	5·1 (2·8–7·2)	0·46 (0·31–0·69)	
≥3	21/47	12/22	33/69	9·4 (7·5–NE)	3·9 (1·8–NE)	0·61 (0·30–1·24)	
Previous endocrine therapy							0·63
Aromatase inhibitor only	58/137	50/70	108/207	9·5 (7·6–13·9)	3·7 (2·1–5·5)	0·39 (0·27–0·57)	
Tamoxifen only	18/51	10/23	28/74	9·5 (7·5–NE)	NE (1·7–NE)	0·61 (0·28–1·33)	
Aromatase inhibitor and tamoxifen	69/159	54/81	123/240	9·5 (7·6–11·2)	4·2 (3·5–7·2)	0·50 (0·35–0·71)	
Sensitivity to previous hormonal therapy							0·13
Yes	108/274	89/136	197/410	10·2 (9·4–11·2)	4·2 (3·5–5·6)	0·42 (0·32–0·56)	
No	37/73	25/38	62/111	7·4 (5·6–9·2)	5·4 (1·9–7·4)	0·64 (0·39–1·07)	
The purpose of most recent therapy							0·39
Neoadjuvant or adjuvant treatment	34/74	24/40	58/114	9·5 (7·4–NE)	5·4 (2·1–10·9)	0·55 (0·32–0·92)	
Metastatic treatment	111/273	90/133	201/406	9·9 (9·2–11·2)	3·9 (3·5–5·6)	0·43 (0·32–0·57)	
Previous chemotherapy							0·22
Neoadjuvant or adjuvant treatment only	59/139	43/74	102/213	11·0 (7·6–NE)	5·6 (3·5–9·3)	0·60 (0·40–0·88)	
Metastatic treatment	53/113	47/64	100/177	7·7 (5·7–9·5)	3·5 (1·9–5·4)	0·43 (0·29–0·64)	
None	33/95	24/36	57/131	10·8 (9·5–NE)	5·4 (3·4–7·3)	0·31 (0·18–0·53)	
PIK3CA status							0·83
Positive	41/85	31/44	72/129	9·5 (5·7–11·2)	3·6 (1·9–5·6)	0·48 (0·30–0·78)	
Negative	71/180	56/86	127/266	9·9 (9·2–13·9)	4·6 (3·4–7·3)	0·45 (0·31–0·64)	
Overall	**145/347**	**114/174**	**259/521**	**9·5 (9·2–11·0)**	**4·6 (3·5–5·6)**	**0·46 (0·36–0·59)**	



CDK 4/6i: Ribo and Abemaciclib



Ribociclib: MONALEESA

Abemaciclib: MONARCH

CDK 4/6 Trial Results

Trial	Line of Tx	Patients	Treatment	HR for PFS	Median PFS, months	ORR
PALOMA-2	1	666	Palbociclib/letro vs placebo/letro	0.58	24.8 vs 14.5	42.1 vs 34.7
PALOMA-3	1	521	Palbociclib/fulvestrant vs. placebo/fulvestrant	0.46	9.5 vs 4.6	19 vs 8
MONALEESA-2	1	668	Ribociclib/NSAI v placebo/NSAI	0.56	NR vs 14.7	40.7 vs 27.5
MONARCH-3	1	493	Abemaciclib + NSAI vs placebo+ NSAI	0.54	NR vs 14.7	59 vs 44
MONARCH-2	1 or 2	669	Abemaciclib + Fulvestrant vs placebo+ Fulvestrant	0.55	16.4 vs 9.3	48.1 vs 21.3

CDK 4/6i AE's

	PALOMA-2			PALOMA-3			MONALEESA-2			MONARCH-3			MONARCH-2		
	Grade (%)			Grade (%)			Grade (%)			Grade (%)			Grade (%)		
Adverse Event	All	3	4	All	3	4	All	3	4	All	3	4	All	3	4
Rash	18	1	--	NR	NR	NR	17	0.6	--	NR	NR	NR	11	1	0
Fatigue	37	2	--	38	2	--	37	2	0.3	40	2	--	40	2.7	--
Diarrhea	26	1	--	19	--	--	35	1.2	--	81	9.5	--	86	13	0
Nausea	35	<1	--	29	--	--	51	2.4	--	38	0.9	--	45	2.7	--
Dec appetite	15	1	--	13	0.9	--	19	1.5	--	25	1.2	--	27	1.1	0
Neutropenia	**80**	56	10	**79**	53	9	**74**	50	9.6	**41**	19	1.5	**46**	24	2.9
Anemia	24	5	<1	26	2.6	0	19	0.9	0.3	28	5.8	--	29	7	0.2
Thrombocytopenia	16	1	<1	19	1.7	0.6	9	0.6	--	NR	NR	NR	16	2	1.4
Alopecia	33	--	--	15	--	--	33	--	--	26	--	--	15	--	--
QTC prolongation	--			--			3.3			--			--		
Inc Creatinine	--			--			--			19	2.1	--	12	0.9	0
VTE/PE					2			2							

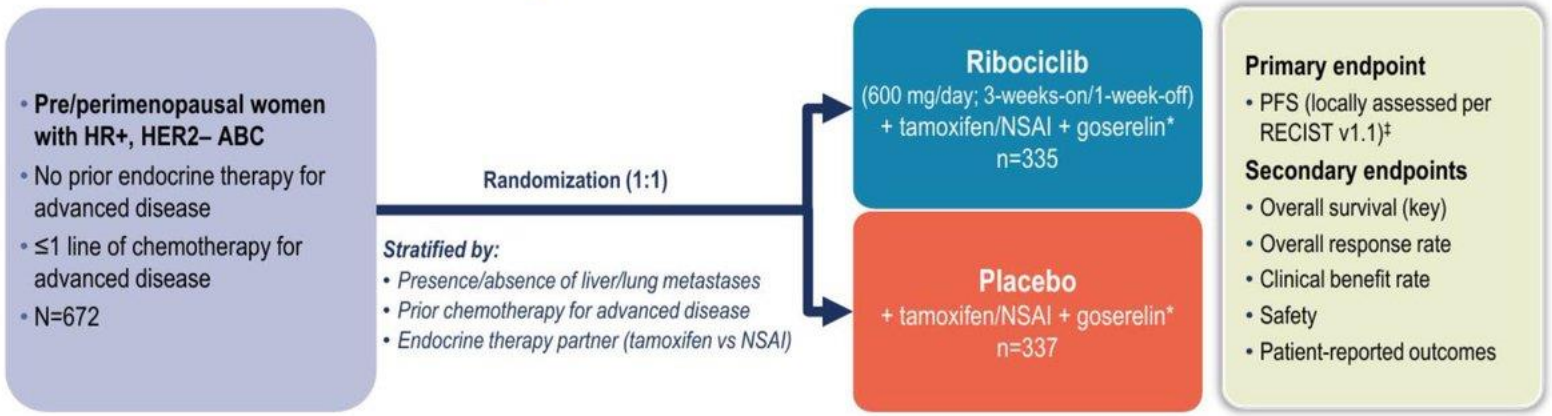
CDK 4/6i: Trial Inclusion Criteria

	PALOMA-2	PALOMA-3	MONALEESA-2	MONARCH-3	MONARCH-2
Criteria	(%)	(%)	(%)	(%)	(%)
Menopause status					
Pre/perimenopausal	0	21	0	0	16
Postmenopausal	100	79	100	100	83
DFI					
De novo metastatic	38	0	34		
<12 months	22	5	1	TFI <36: 28	
>12 months	40	95	65	TFI>36: 62	
Prior NAC	48	40	44	40	60
Prior Tx of ABC	0	38	0	0	38

MONALEESA-7: Premenopausal women

San Antonio Breast Cancer Symposium, December 5–9, 2017

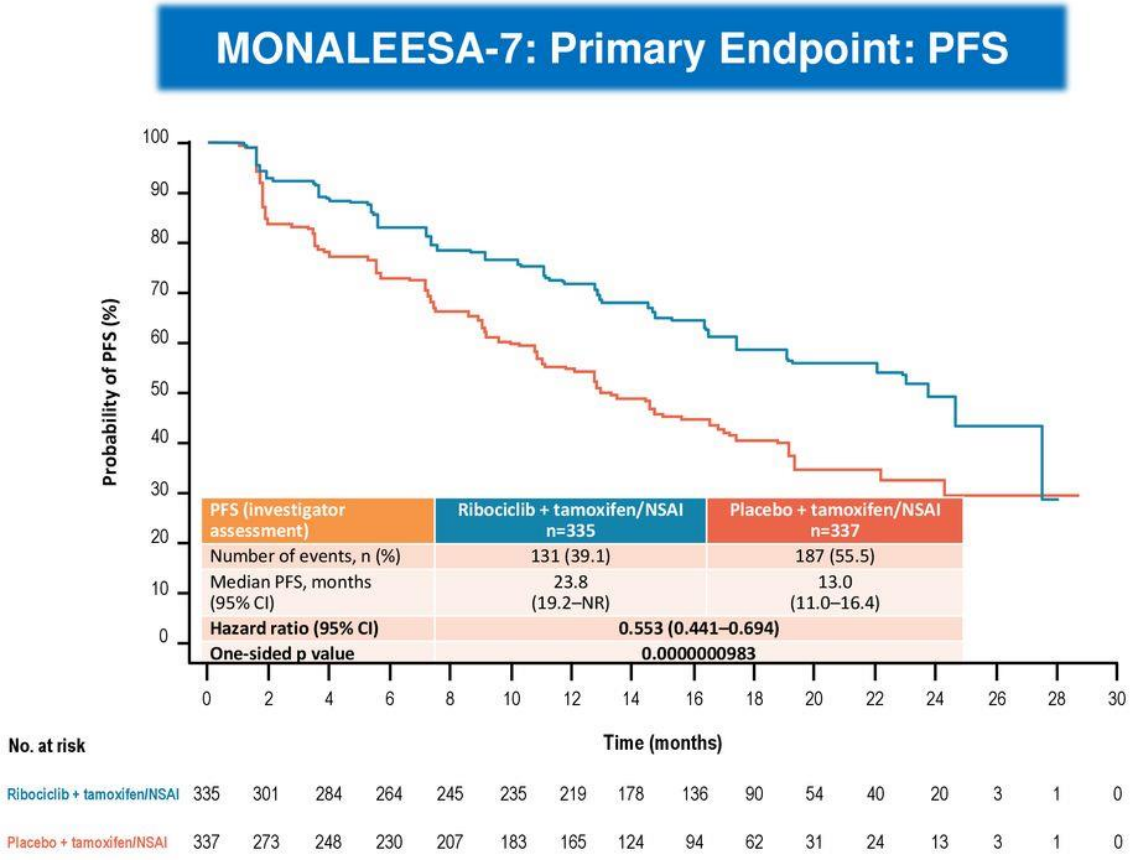
MONALEESA-7: Phase III placebo-controlled study of ribociclib and tamoxifen/NSAI + goserelin



- Tumor assessments were performed every 8 weeks for 18 months, then every 12 weeks thereafter
- Primary analysis planned after ~329 PFS events
  - 95% power to detect a 33% risk reduction (hazard ratio 0.67) with one-sided α=2.5%, corresponding to an increase in median PFS to 13.4 months (median PFS of 9 months for the placebo arm[1,2]), and a sample size of 660 patients

NSAI, non-steroidal aromatase inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors.
*Tamoxifen = 20 mg/day; NSAI: anastrozole = 1 mg/day or letrozole = 2.5 mg/day; goserelin = 3.6 mg every 28 days;
‡PFS by Blinded Independent Review Committee conducted to support the primary endpoint.
1. Klijn JG, *et al. J Clin Oncol* 2001;19:343–353; 2. Mourisden H, *et al. J Clin Oncol* 2001;19:2596–2606.

MONALEESA-7



Triphaty D, SABCS 2017

CDK 4/6 AE's: Monitoring

Agent	Most Common AE's	Required monitoring
Palbociclib	Incidence >10%: Neutropenia, leukopenia, infections, fatigue, nausea, stomatitis, anemia, alopecia, diarrhea, rash, decreased appetite, pyrexia	CBC
Ribociclib	Incidence >20%: Neutropenia, nausea, fatigue, diarrhea, leukopenia, alopecia, constipation, headache, back pain	ECG for QTc prolongation(day 0, 14, and 28), electrolytes, LFTs, CBC
Abemaciclib	Incidence >20%: Diarrhea, neutropenia, nausea, abdominal pain, infections, fatigue, increased creatinine, anemia, thrombocytopenia, decreased appetite	CBC, LFTs, Creatinine, VTE/PE

CDK 4/6: Dosing for Neutropenia

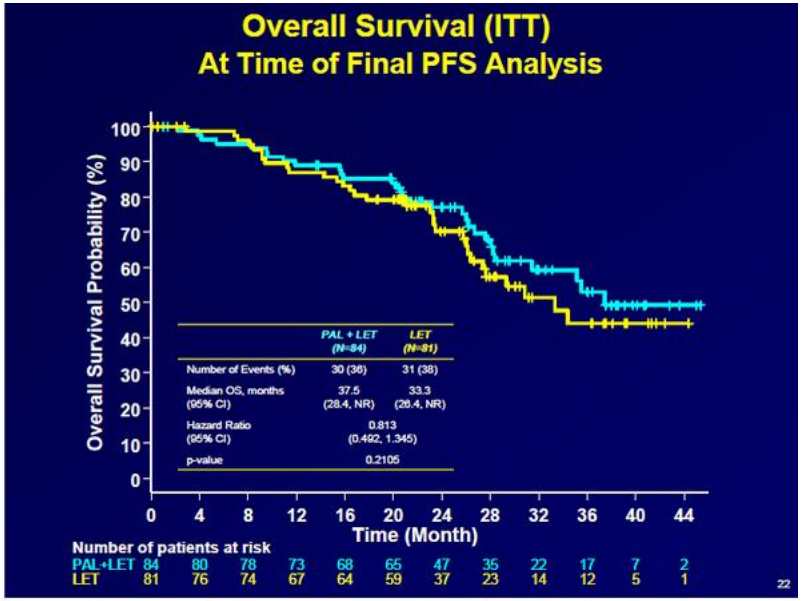
CDK 4/6 i	GRADE 1 or 2 (ANC 1000-<LLN)	Grade 3 (ANC 500-1000)	Grade 3 with Febrile Neutropenia	Grade 4 (ANC<500)
Palbociclib: CBC at baseline, day 1 each cycle, day 14 of cycles 1,2	No dose adjustment	Interrupt until grade 2, resume at lower dose level	Interrupt until ANC>1000, resume at lower dose level	Interrupt until ANC>1000, resume at lower dose level
Ribociclib: CBC at day 0, every 2 weeks for cycles 1,2 then every 4 weeks	No dose adjustment	Interrupt until ANC>1000, resume at lower dose	Interrupt until ANC>1000, resume at lower dose	Interrupt until ANC>1000, resume at lower dose level
Abemaciclib: CBC day 0, every 2 weeks x 2 months, then monthly	No dose adjustment	Interrupt until ANC >1000, resume at prior dose	No recommendation	Interrupt until ANC>1000, resume at lower dose level

CDK 4/6: Abemaciclib-Associated Diarrhea

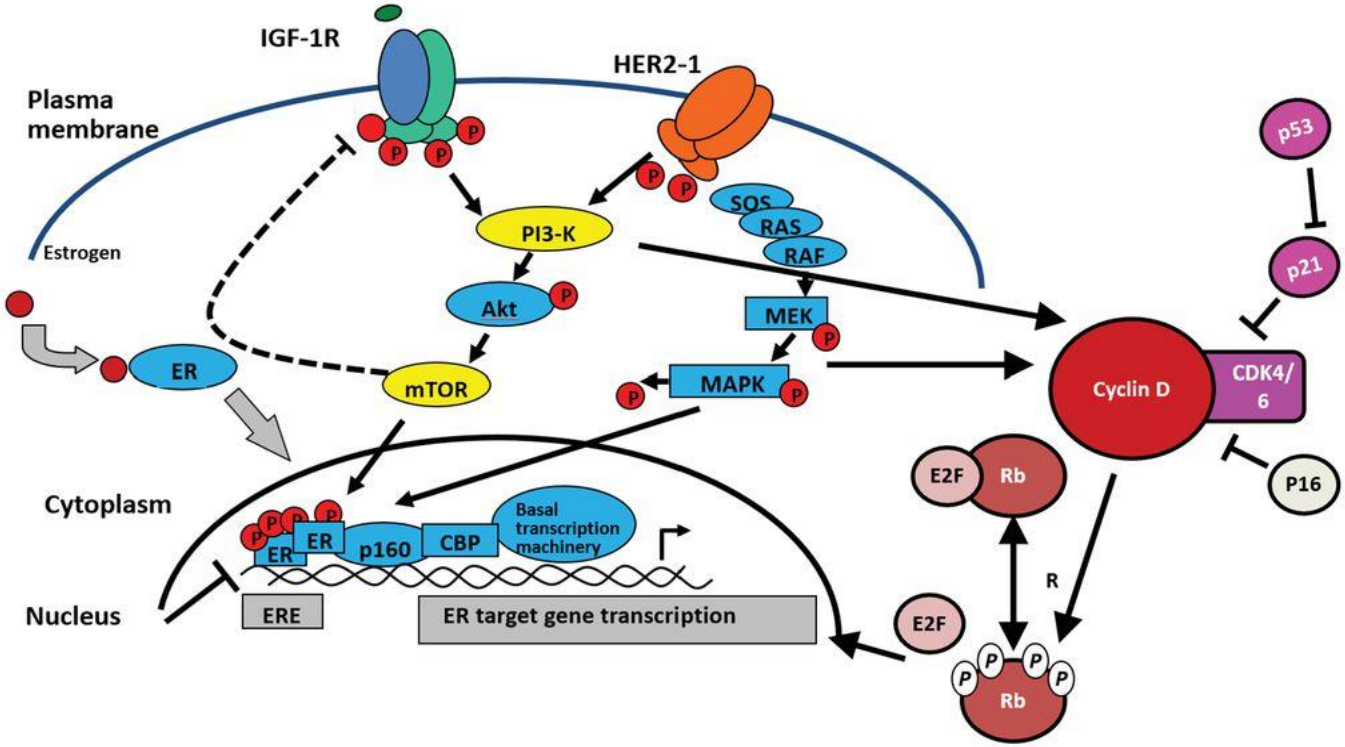
At first sign of loose stools, start treatment with anti-motility agent, increase oral fluid intake.	
Grade 1	No dose modification
Grade 2	If diarrhea dose not resolve to grade 1 in 24 hours, interrupt dose until resolution, resume at prior dose
Grade 2 that persists or recurs at initial dose despite maximal supportive measures	Interrupt until resolves to < grade 1, resume at next lower dose
Grade 3 or 4 or requires hospitalization	Interrupt until resolves to < grade 1, resume at next lower dose

CDK 4/6, Remaining Questions

- Crossover not permitted, optimal sequencing undetermined: is upfront combination therapy superior to sequent ET followed by combination
- Quality of life indicators yet to be reported
- Overall survival benefit not yet shown in pivotal trials
- Versus chemotherapy
- Predictive biomarkers?



Pathways



Cross-talk between Estrogen (ER) and epidermal growth factor receptor (EGFR)/insulin-like growth factor 1 receptor (IGF-1R) signaling pathway and cyclin-dependent kinase (CDK)4/6 function.
From Springer Nature: Di Cosimo S and Baselga J. 2010.
HER2-1, human epidermal growth factor receptor 2; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase.

ET + MTOR inhibition: BOLERO-2

Exemestane ± Everolimus in AI-Refractory Advanced BC: BOLERO-2 Trial

- Randomized, double-blind, phase 3 trial

Postmenopausal women with hormone receptor-positive, HER2- ABC refractory to letrozole or anastrozole (N = 724)

R

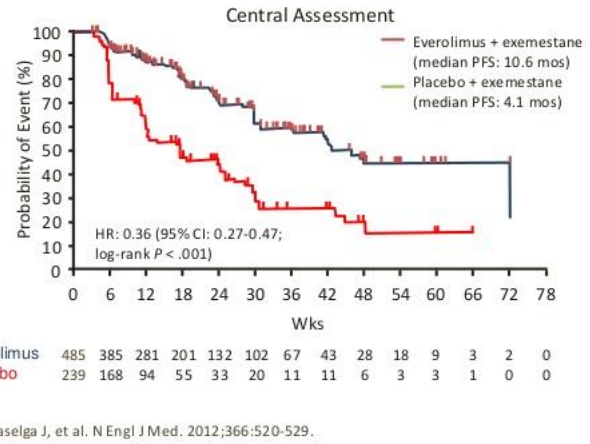
- Everolimus PO 10 mg/d + exemestane PO 25 mg (n = 485)
- Placebo + exemestane PO 25 mg/d (n = 239)

	Everolimus + Exemestane	Placebo + Exemestane	HR (95% CI)	*P* Value
Median PFS, mo				
• Interim analysis	6.9	2.8	0.43 (0.35, 0.54)	<.001
• 18-mo follow-up	7.8	3.2	0.45 (0.38, 0.54)	<.0001
Serious AEs, %	23	12		

- Most common grade 3/4 AEs with exemestane + everolimus: stomatitis, anemia, dyspnea, hyperglycemia, fatigue, pneumonitis

Basegla J, et al. *N Engl J Med.* 2012;366:520-529; Yardley D, et al. *Adv Ther.* 2013;30:870-884.

BOLERO-2: Everolimus + Exemestane Improves PFS in HR+ MBC



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

ET + MTOR inhibition: BOLERO-2

BOLERO-2: Most Common Grade 3/4 Adverse Events

	Everolimus + Exemestane (N = 482), %			Placebo + Exemestane (N = 238), %		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Stomatitis	56	8	0	11	1	0
Fatigue	33	3	< 1	26	1	0
Dyspnea	18	4	0	9	1	< 1
Anemia	16	5	< 1	4	< 1	< 1
Hyperglycemia	13	4	< 1	2	< 1	0
Aspartate aminotransferase level increased	13	3	< 1	6	1	0
Pneumonitis	12	3	0	0	0	0

AE = adverse event; AST = aspartate aminotransferase

a. Baselga J, et al. *N Engl J Med*. 2012;366:520-529.[18]

TAMRAD Trial

TAMRAD Phase II Study Schema

Eligibility

- Metastatic breast cancer
- Menopausal condition
- Hormone receptor-positive; HER2-negative
- Prior exposure to aromatase inhibitor (AI)

R

- Tamoxifen (n = 57)
- Tamoxifen + everolimus (n = 54)

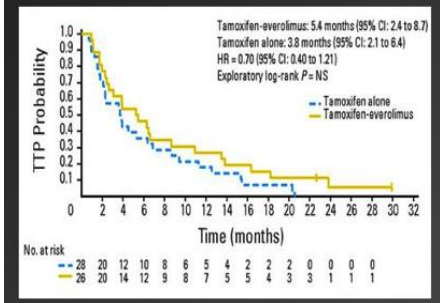
Primary endpoint:
Clinical benefit rate (CBR) at 6 months; a gain of 20% in CBR required to warrant further study of tamoxifen/everolimus combination.

Secondary endpoints: Time to progression (TTP), overall survival, objective response rate, toxicity.

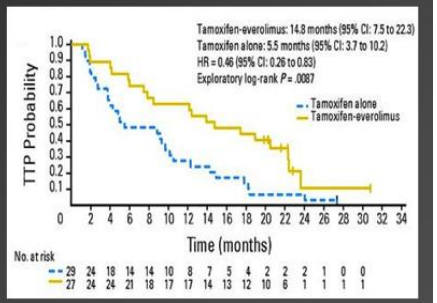
Bachelot T et al. *Proc SABCS* 2010;Abstract S1-6.

The TAMRAD trial: TTP results by level of response to prior aromatase inhibitor therapy

Primary resistance



Secondary resistance



Bachelot T et al, J Clin Oncol 30: 2718-24, 2012

Alpha-specific PI3Ki

- SOLAR-1: phase III: Alpelisib + Fulvestrant, PD after prior AI
- SANDPIPER: phase III: Taselisib + Fulvestrant, PD after prior AI

SOLAR-1

A phase 3 study of alpelisib (ALP) plus fulvestrant (FUL) in men and postmenopausal women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) ABC progressing on or after aromatase inhibitor (AI) therapy: SOLAR-1.

- Men or postmenopausal women with HR+/ HER2–, locally advanced or metastatic breast cancer
- Progression after or during AI
- N=560

Randomization (1:1)

Stratified by visceral disease and previous treatment with CDK 4/6i

FUL 500 mg i.m. + ALP 200 mg/day n= 280

FUL 500 mg i.m. + Placebo n=280

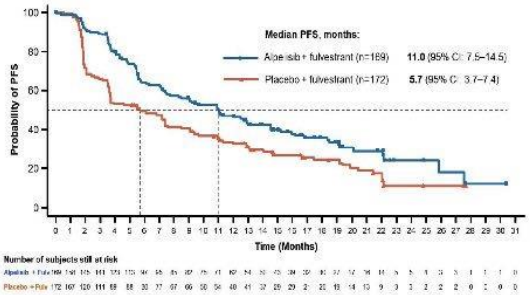
Primary endpoint
- PFS (locally assessed per RECIST v1.1)

Key secondary endpoint
- OS

- Tumor assessments will be performed every 8 week

San Antonio Breast Cancer Symposium[K], December 4-8, 2018

Primary Endpoint: Locally Assessed PFS in the *PIK3CA*-mutant Cohort[1,a]

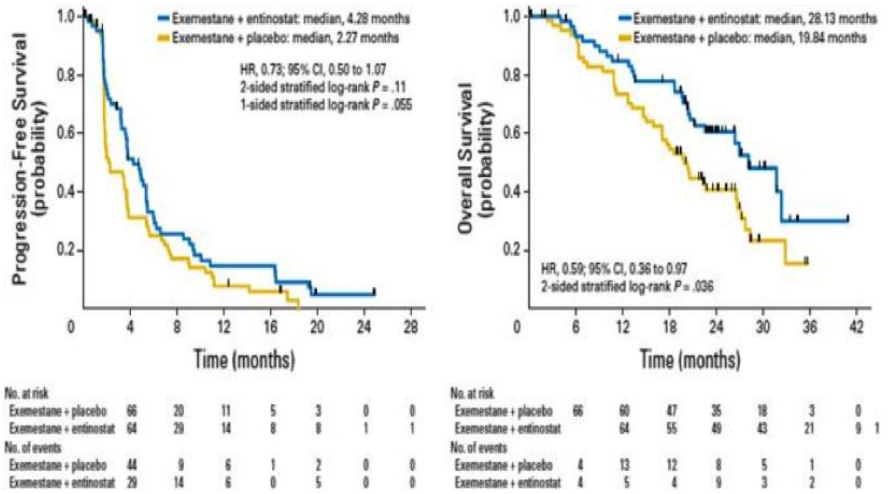


Data cut-off: Jun 12, 2018	ALP + FUL (n = 169)	PBO + FUL (n = 172)
Number of PFS events, n (%)	103 (60.9)	129 (75.0)
Progression	99 (58.6)	120 (69.8)
Death	4 (2.4)	9 (5.2)
Censored	66 (39.1)	43 (25.0)
Median PFS (95% CI)	11.0 (7.5-14.5)	5.7 (3.7-7.4)
HR (95% CI)	0.65 (0.50-0.85)	
One-sided *P* value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

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.
At final PFS analysis, superiority was declared if one-sided, stratified log-rank test P value was ≤ 0.0199 (Haybittle–Peto boundary).
[a] Mutation status determined from tissue biopsy.
1. Andre F, et al. ESMO 2018. Abstract LBA3 [oral].

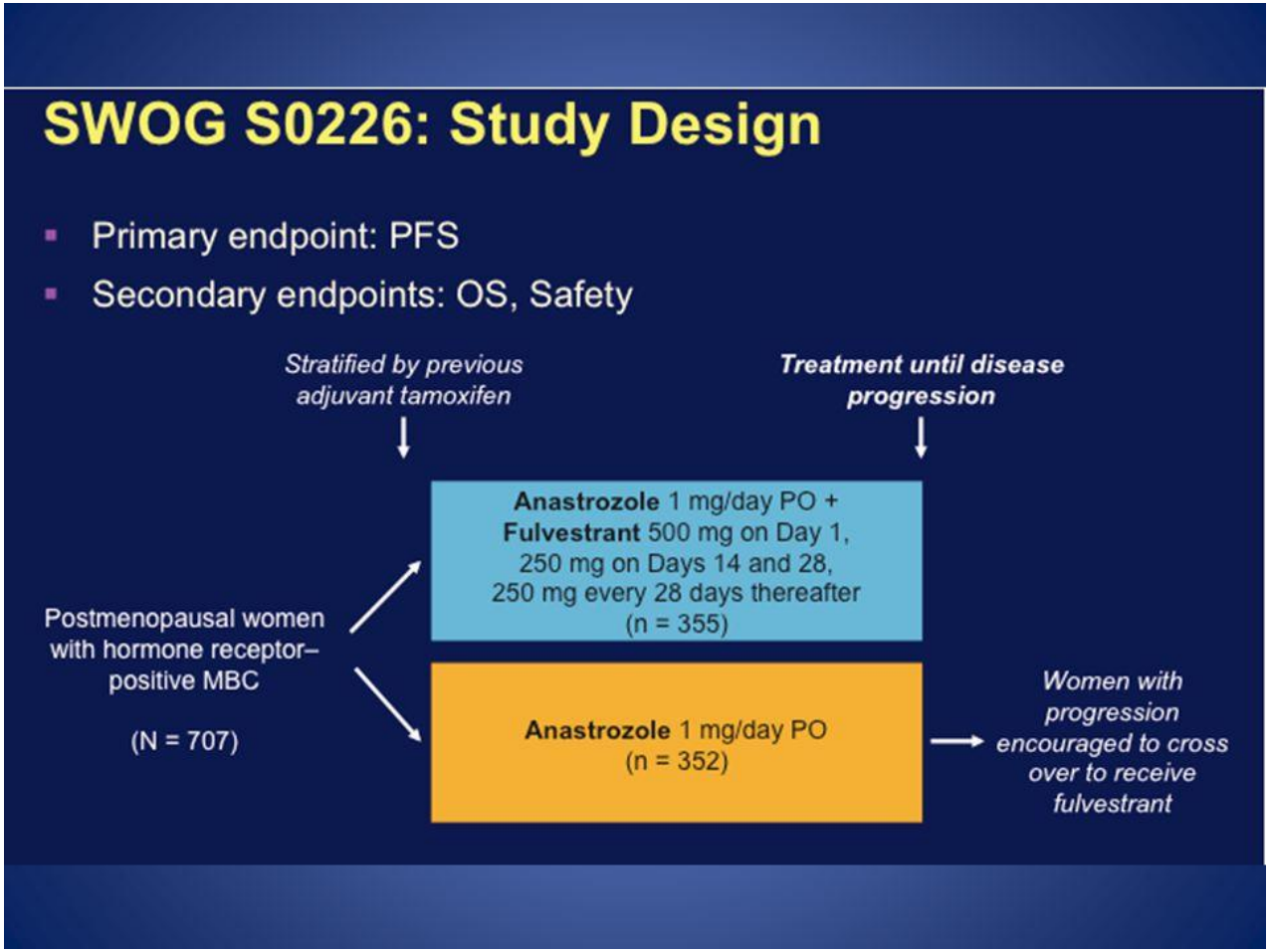
HDAC Inhibitors

- Potential mechanism of ET resistance is transcriptional repression of ER by HDAC
- HDACi lower ER suppression transcription, degrade cyclin D1
- HDACi (vorinostat, entinostat) plus AI under study

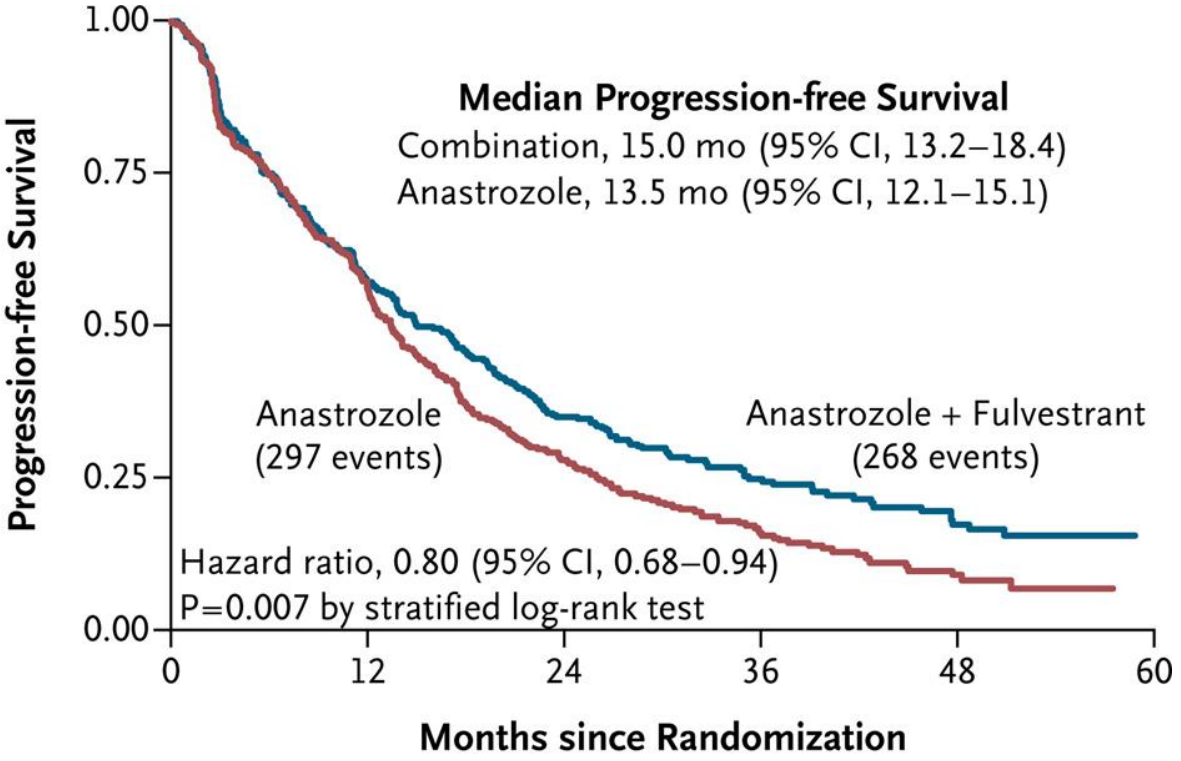


ENCORE301. Yardley, JCO 2013

SWOG S0226

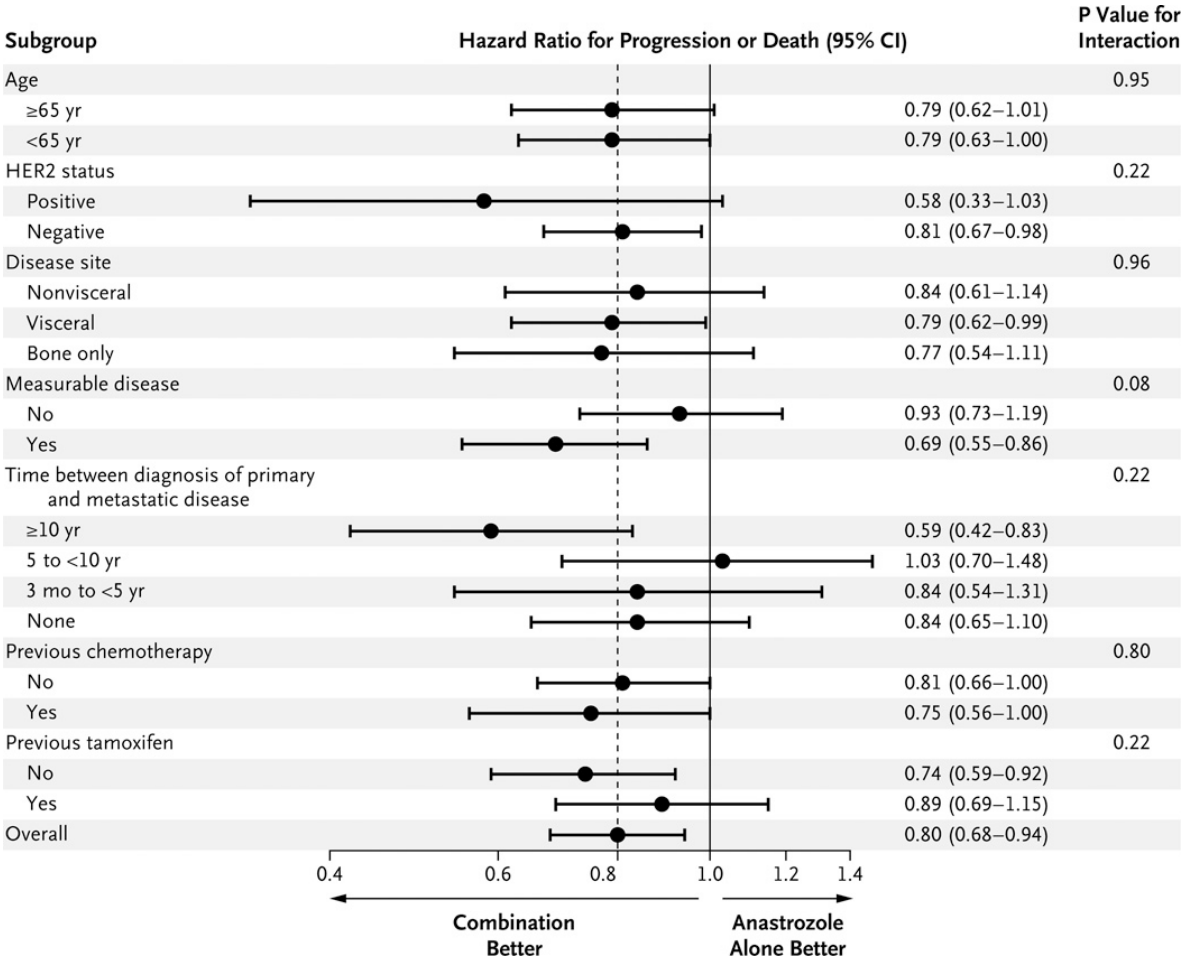

SWOG S0226: Study Design
Primary endpoint: PFS
Secondary endpoints: OS, Safety
Stratified by previous adjuvant tamoxifen
Treatment until disease progression
Postmenopausal women with hormone receptor–positive MBC
(N = 707)
Anastrozole 1 mg/day PO + Fulvestrant 500 mg on Day 1, 250 mg on Days 14 and 28, 250 mg every 28 days thereafter (n = 355)
Anastrozole 1 mg/day PO (n = 352)
Women with progression encouraged to cross over to receive fulvestrant

SWOG S0226



No. at Risk						
Anastrozole + fulvestrant	349	199	114	53	21	8
Anastrozole	345	193	92	39	11	3

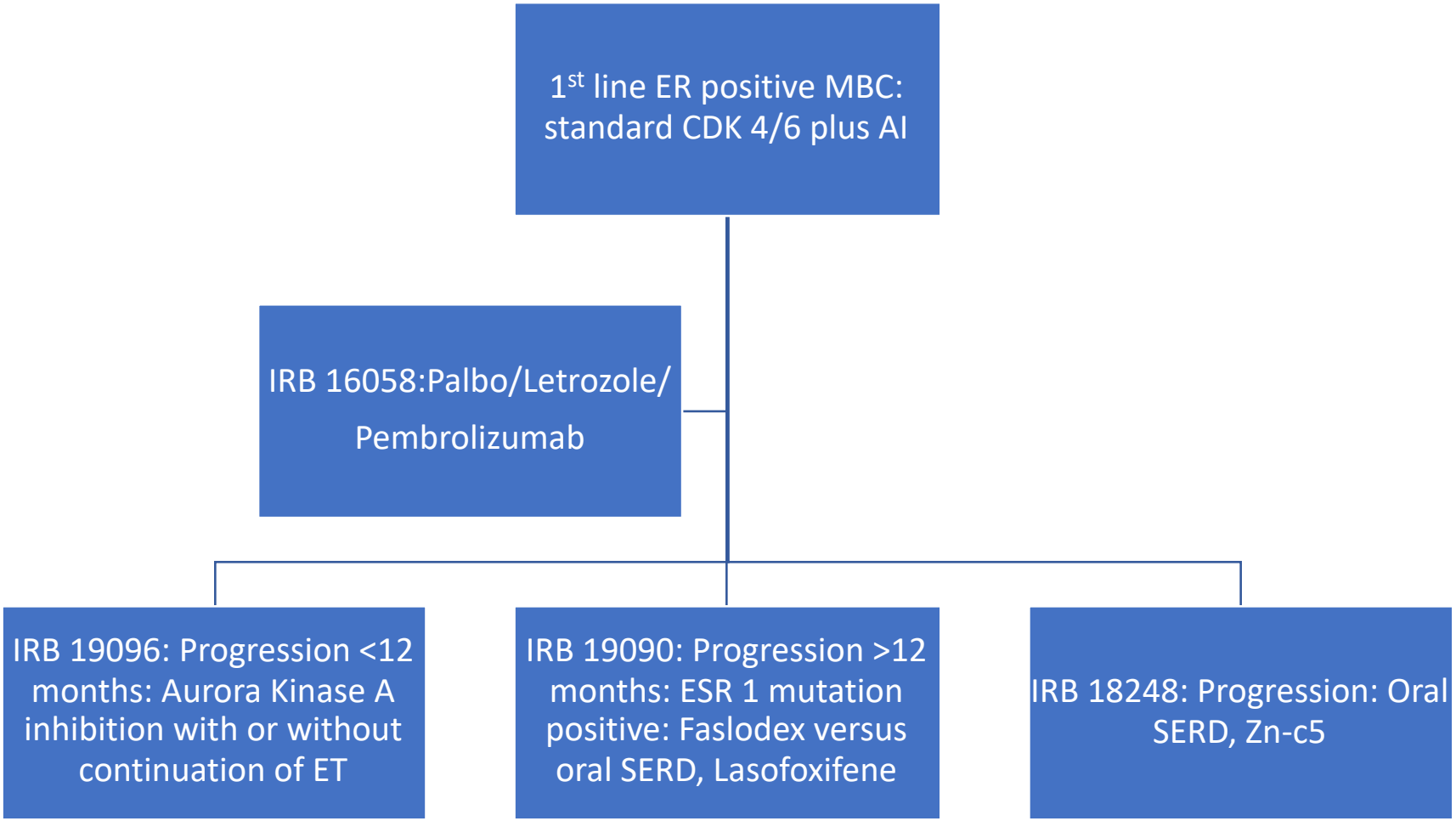
SWOG S0226



Conclusions

- CDK 4/6 inhibitors with standard ET are the standard of care for ER positive MBC patients.
  - Increased response rate and PFS in all patient subgroups
  - Acceptable toxicity profile
  - No survival benefit demonstrated yet
- Role of everolimus after CDK 4/6 failure unclear
- CDK 4/6 versus upfront chemotherapy in visceral crisis
- Utility in patients with CNS metastases
- Future: PI3Kalpha, aurKi

COH Portfolio



THANKS!