Endocrine Therapy for Advanced Breast Cancer: Current and Future Strategies

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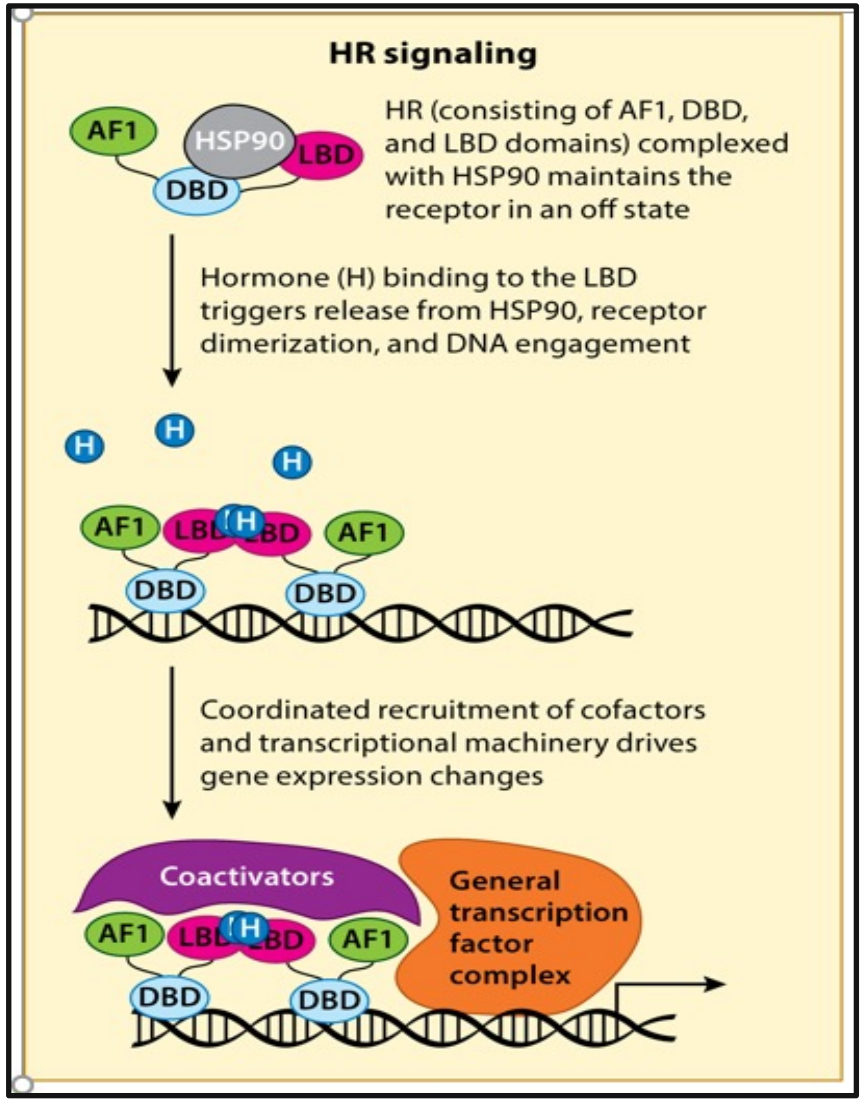
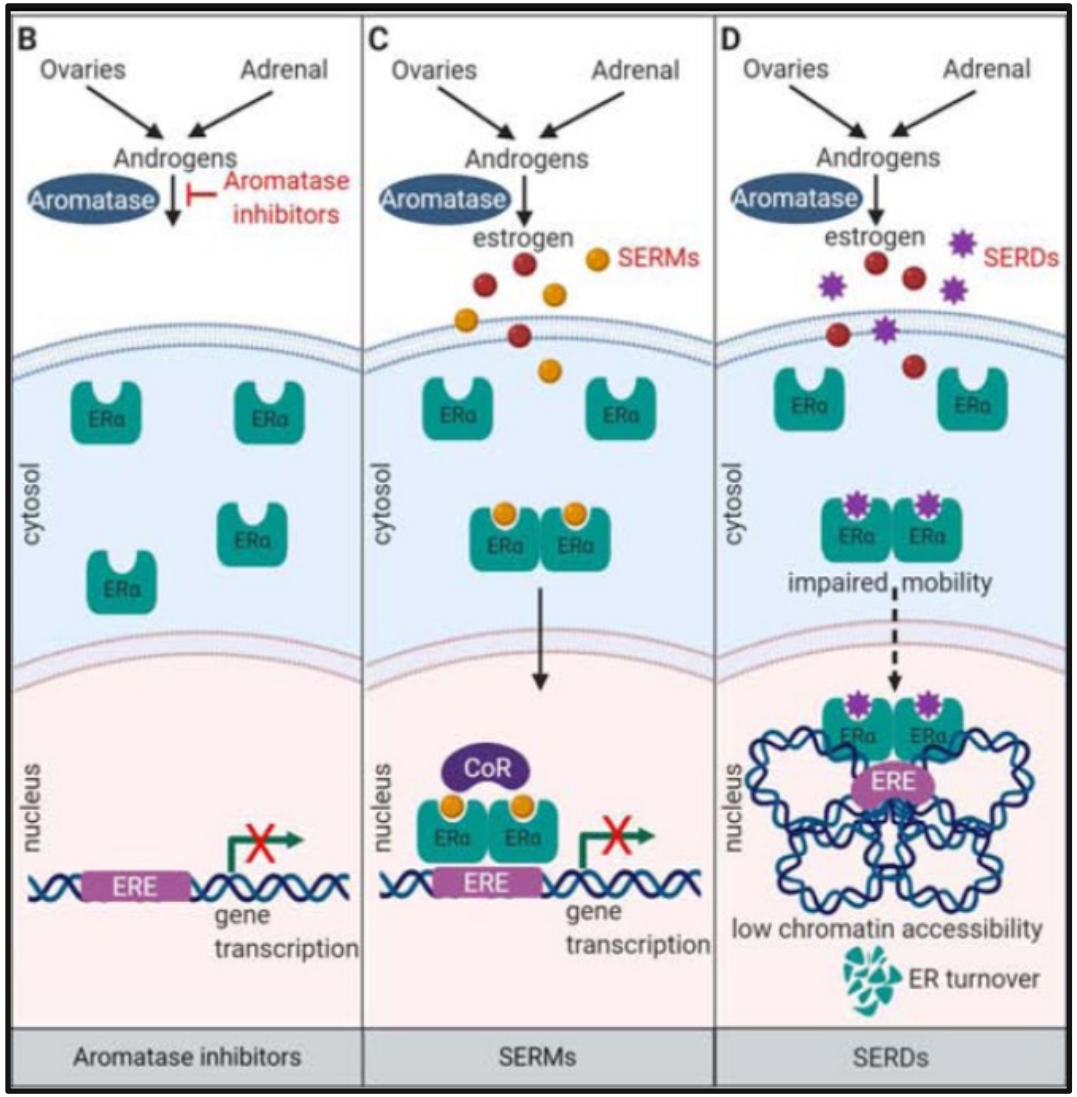
Hormone Receptor Signaling and Mechanism of Action of Approved Drugs Targeting ER





Slide credit: Komal Jhaveri, MD

Metcalfe C et al Annual Review Cancer Biology 2018; Hanker et al Cancer Cell 2020

Limitations of Currently Approved Endocrine Agents

Aromatase Inhibitors

- Acquired *ESR1* mutations
- Confer AF2 activity in the absence of estrogen
- Toxicity profile

Tamoxifen

- Partial ER agonist, blocks AF2 but allows activation of AF1
- Manifest as weaker ER suppression
- Toxicity profile

Fulvestrant

- Inconvenience: IM Injection
- Poor PK
- Efficacy is dose dependent/Incomplete ER degradation
- Single agent activity limited post CDK4/6 inhibitors
- Activity limited in *ESR1* Y537S

Slide credit: Komal Jhaveri, MD

McDonnell et al JCO 2021; Lindeman GJ et al ASCO 2021; Toy et al Cancer Discovery 2017;

What Has Been Established for HR+/HER2- MBC, as of 2023

- **CDK4/6 inhibitors (CDK4/6i) + endocrine therapy (ET) are THE gold standard therapy in first- or second-line setting for HR+ HER2- MBC**
  - The 3 agents similarly improve PFS[1-7]
  - Overall survival improved compared to single-agent ET for ribociclib (3 trials: combined with AI/ovarian suppression in pre/peri-menopausal,[3] combined with AI or fulvestrant (FULV) in postmenopausal)[2,7] and abemaciclib (1 trial, combined with FULV in pre- or postmenopausal)[6]
  - Progression-free survival with CDK4/6i + ET appears to be similar or improved compared with chemotherapy (capecitabine) in second-line setting[8,9] and superior to combination chemotherapy in the first-line setting[10].

1. PALOMA-2: Finn R, et al. *N Engl J Med*. 2016;375:1925-1936.
2. MONALEESA-2: Hortobagyi G, et al. *N Engl J Med*. 2016;375:1738-1748; Hortobagyi G, et al. *Ann Oncol*. 2018;29:1541-1547; Hortobagyi G. et al. ESMO 2021. Abstract LBA17_PR.
3. MONALEESA-7: Tripathy D, et al. *Lancet Oncol.* 2018;19:904-915; Im S-A, et al. *N Engl J Med*. 2019;381:307-316. [Note PFS/OS data reported for approved AI subset]
4. MONARCH-3: Goetz M, et al. *J Clin Oncol*. 2017;35:3638-3646; Johnson S, et al. NPJ *Breast Cancer. 2019;5:5*.
5. PALOMA-3: Turner NC, et al. *N Engl J Med*. 2015;373:209-219; Cristofanilli M, et al. *Lancet Oncol*. 2016;17:425-439; Turner NC, et al. *N Engl J Med*. 2015;373:1672-1673.
6. MONARCH-2: Sledge G, et al. *J Clin Oncol*. 2017;35:2875-2884; Sledge G, et al. *JAMA Oncol.* 2020;6:116-124.
7. MONALEESA-3: Slamon D, et al. *J Clin Oncol.* 2018;36:2465-2472; Slamon D, et al. *New Engl J Med*. 2020;382:514-524; Slamon DJ, et al. ASCO 2021. Abstract 1001.
8. Park YH, et al. *Lancet Oncol.* 2019;20:1750-1759.
9. PEARL: Martin M, et al. *Ann Oncol.* 2021;32:488-499; Martin Jimenez M, et al. ESMO 2021. Abstract 229MO.
10. RIGHT-CHOICE: Lu Y, et al. SABCS 2022.. Abstract GS1-10.

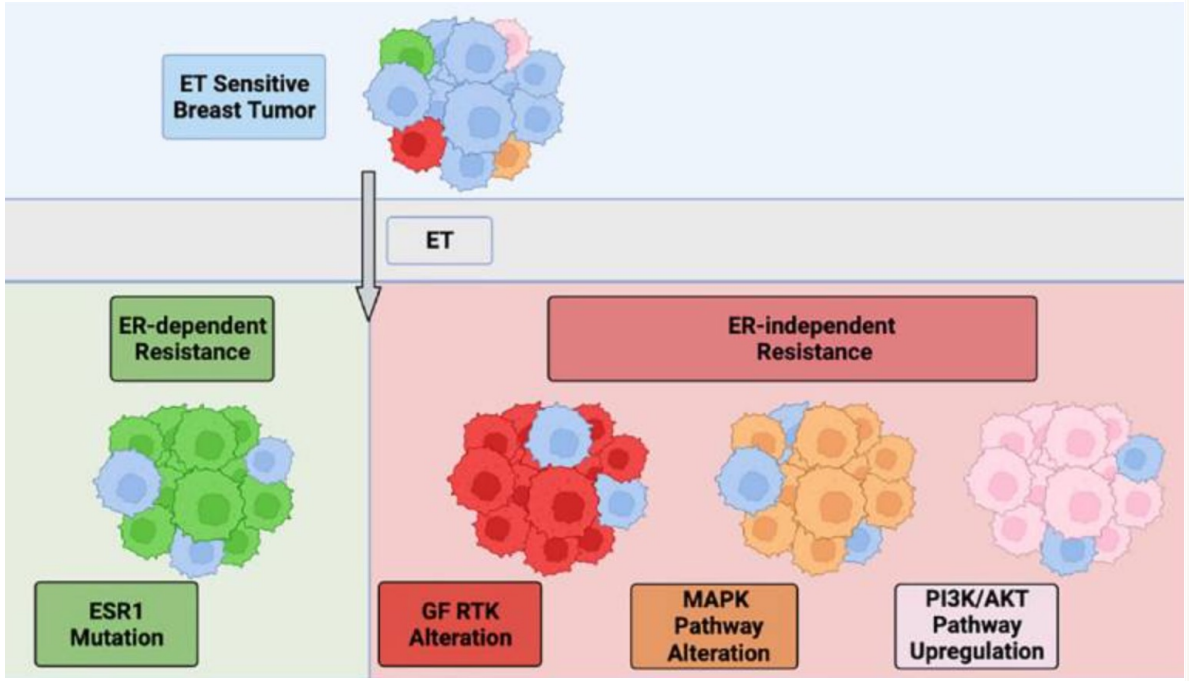
Results for Pivotal CDK 4/6 Inhibitor Trials

Trial	CDK Inhibitor	Line of Therapy (Endocrine Rx)	Menopausal Status	PFS HR	Statistical Significance	OS HR	Statistical Significance
PALOMA-2[1]	Palbociclib	1st Line/AI	Post	0.56	Yes	0.96	No
MONALEESA-2[2]	Ribociclib	1st Line/AI	Post	0.57	Yes	0.76	Yes
MONALEESA-7[3]	Ribociclib	1st Line/AI or Tam	Pre/Peri	0.55	Yes	0.70	Yes
MONARCH-3[4]	Abemaciclib	1st Line/AI	Post	0.54	Yes	0.75	No (@IA2)
PALOMA-3[5]	Palbociclib	2nd Line/Fulv	Pre/Post	0.46	Yes	0.81	No
MONARCH-2[6]	Abemaciclib	2nd Line/Fulv	Pre/Post	0.55	Yes	0.78	Yes
MONALEESA-3[7]	Ribociclib	1st /2nd Line/Fulv	Pre/Post	0.59	Yes	0.72	Yes

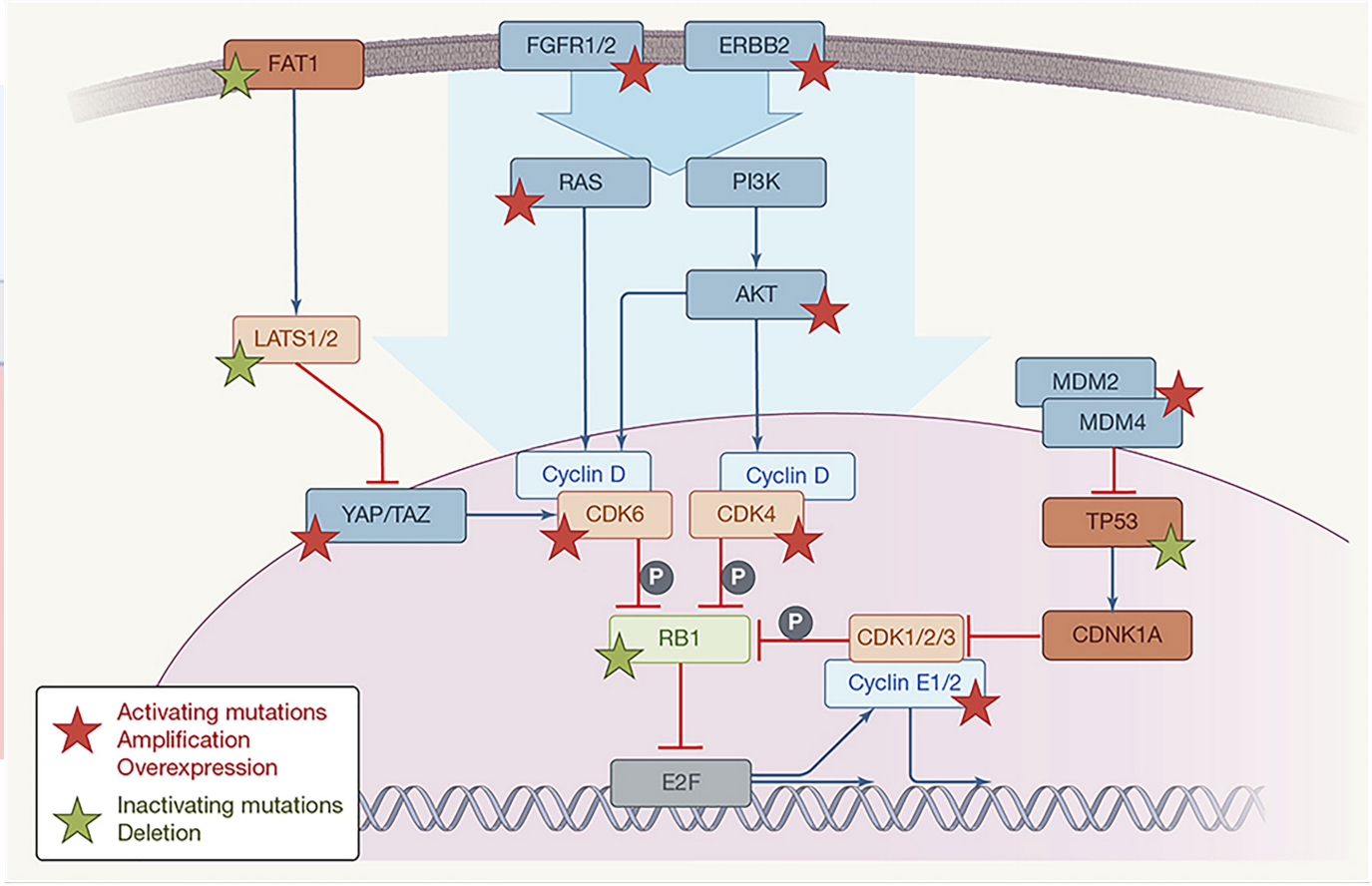
AI indicates aromatase inhibitor; Fulv, fulvestrant; IA2, interim analysis 2; NR, not reported; Rx, therapy.

1. PALOMA-2: Finn R, et al. *N Engl J Med*. 2016;375:1925-1936; Rugo H, et al. *Breast Cancer Res Treat*. 2019;174:719-729. Finn R, et al. ASCO 2022. LBA1003. **2.** MONALEESA-2: Hortobagyi G, et al. *N Engl J Med*. 2016;375:1738-1748; Hortobagyi G, et al. *Ann Oncol*. 2018;29:1541-1547; Hortobagyi G. et al. ESMO 2021. Abstract LBA17_PR. **3.** MONALEESA-7: Tripathy D, et al. *Lancet Oncol*. 2018;19:904-915; Im S-A, et al. *New Engl J Med*. 2019;381:307-316. **4.** MONARCH-3: Goetz M, et al. *J Clin Oncol*. 2017;35:3638-3646; Johnson S, et al. NPJ *Breast Cancer. 2019;5:5*. Goetz MP, et al. ESMO 2022. Abstract LBA 15. **5.** PALOMA-3: Turner NC, et al. *New Engl J Med*. 2015;373:209-219; Cristofanilli M, et al. *Lancet Oncol*. 2016;17:425-439; Turner NC, et al. *New Engl J Med*. 2015;373:1672-1673. **6.** MONARCH-2: Sledge G, et al. *J Clin Oncol*. 2017;35:2875-2884; Sledge G, et al. *JAMA Oncol*. 2020;6:116-124**. 7.** MONALEESA-3: Slamon D, et al. *J Clin Oncol*. 2018;36:2465-2472; Slamon D, et al. *New Engl J Med*. 2020;382:514-524.

Resistance to ET + CDK4/6i: Now a High Unmet Need



ER dependent and independent mechanism of resistance

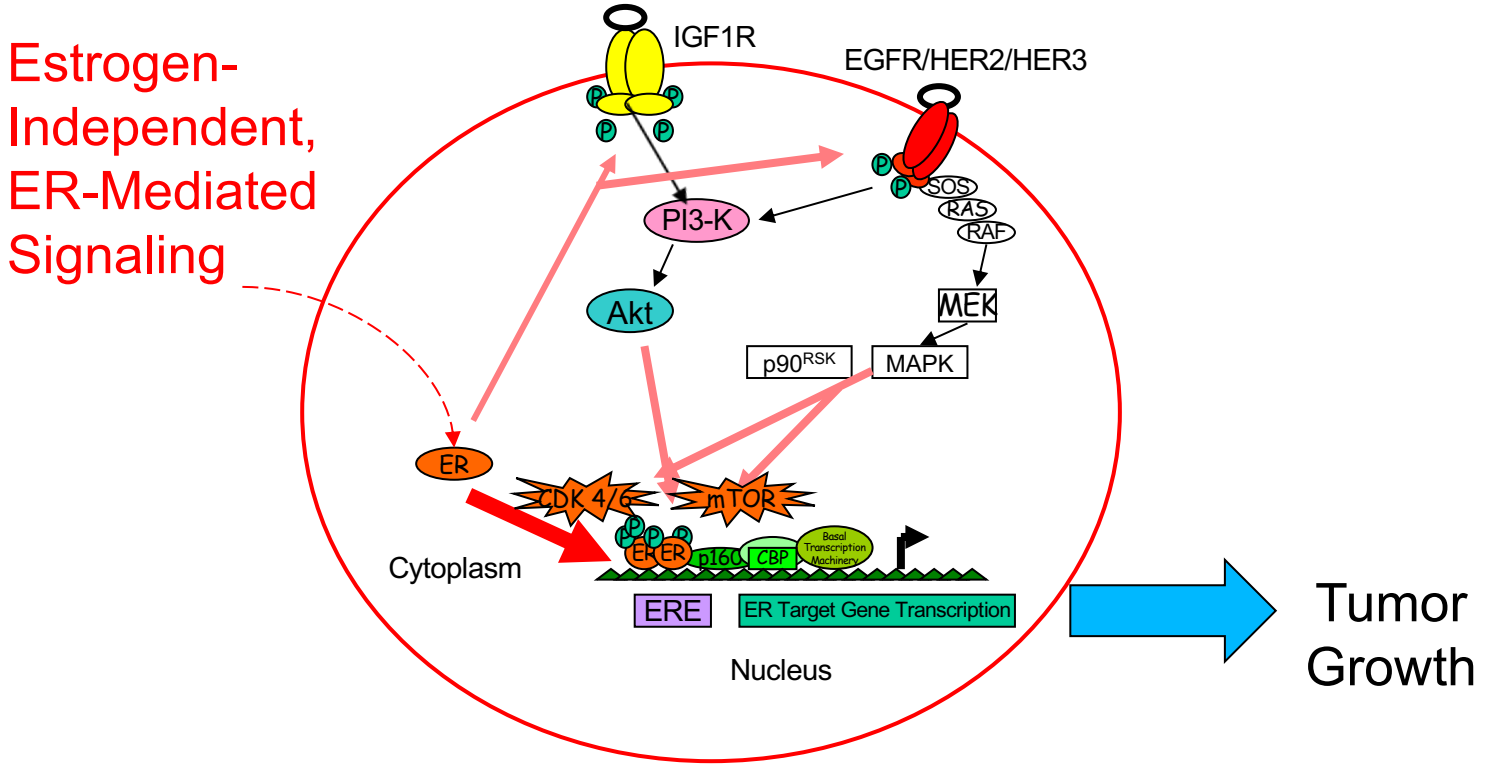


Major Mechanisms of Resistance to CDK4/6 Inhibitors

Lloyd MR, et al. *Ther Adv Med Oncol* 2022, Vol. 14: 1–25
Álvarez-Fernández M, Malumbres M. *Cancer Cell*. 2020;37:514-529.

Slide credit: Hope Rugo, MD

Endocrine Therapy Resistance: Potential Factors to Consider



- ER pathway is still active and disease progression due to estrogen-independent but estrogen-receptor mediated signaling...*ESR1* mutations…

Johnston SR. *J Natl Cancer Inst*. 2015;107:djv212.

ESR1 Mutations in Breast Cancer

- Rare in primary tumors <1%
- Highly enriched in MBC

Trial	Study Treatment	ER+ MBC Patient Population	*ESR1* Mut, %
MONALEESA-2[1]	Letrozole ± ribociclib	1st line	4.0
BOLERO-2[2]	Exemestane ± everolimus	After PD on ET	28.8
FERGI[3]	Fulvestrant ± pictilisib	After PD on ET	~40.0
PALOMA-3[4]	Fulvestrant ± palbociclib	After PD on ET	25.3
SOFeA[5]	Fulvestrant ± anastrozole	After PD on ET	39.1

1. Hortobagyi. Ann Oncol. 2018;29:1541. 2.Chandarlapaty. JAMA Oncol. 2016;2:1310. 3.Spoerke. Nat Commun. 2016;7:11579. 4. Cristofanilli. Lancet Oncol. 2016:17:425. 5. Fribbens. JCO. 2016;34:2961.

FDA Approves Elacestrant for ER+/HER2- Advanced Breast Cancer

January 27, 2023
Jonah Feldman

Elacestrant has recieved FDA approval for the treatment of patients with estrogen receptor-positive/HER2-negative advanced or metastatic breast cancer.

The FDA has approved elacestrant [redacted], an oral selective estrogen receptor degrader (SERD), for use in patients with estrogen receptor (ER)-positive/HER2-negative advanced or metastatic breast cancer.[1]

1. FDA approves elacestrant for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer. News Release. FDA. January 27, 2023. Accessed January 27, 2023. https://bit.ly/3WHsEq8

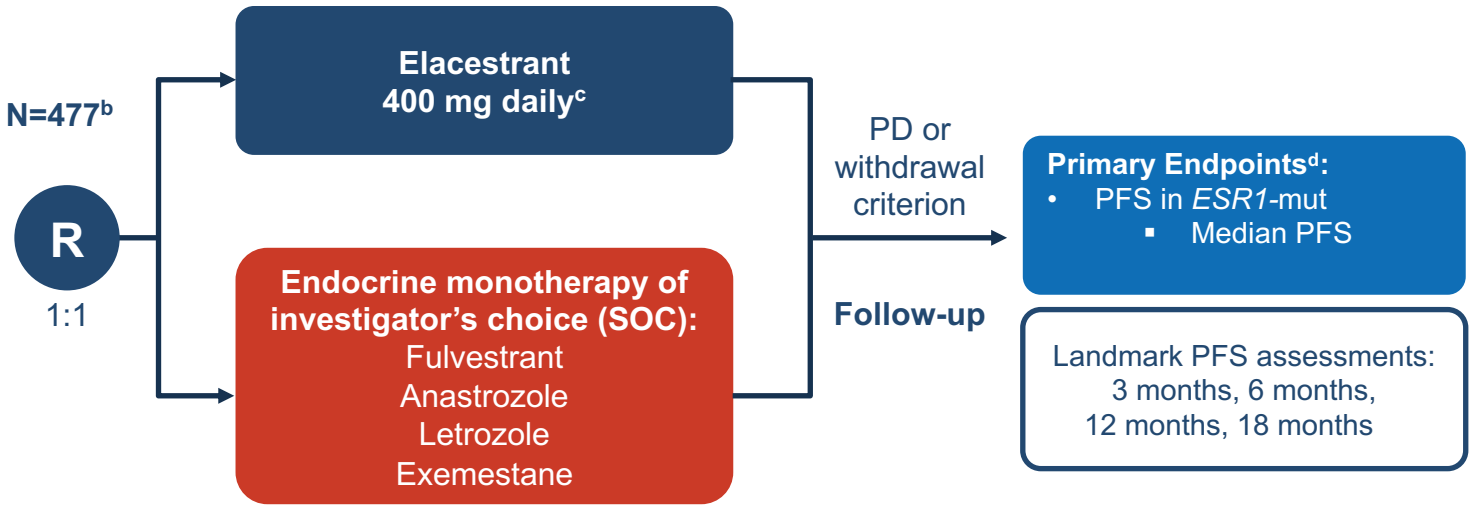
Oral SERD Trial Landscape in Pretreated mBC

	EMERALD[1]	SERENA-2[2]	EMBER-3[3]	AMEERA-3[4-6]	acelERA[6-9]
Treatment	**Elacestrant**	**Camizestrant**	**Imlunestrant** ± abemaciclib	**Amcenestrant**	**Giredestrant**
Control arm	Fulvestrant/AIs	Fulvestrant	Fulvestrant/exemestane	Fulvestrant/AIs/ tamoxifen	Fulvestrant/AIs
Phase (n)	Phase 3 (478)	Phase 2 (240)	Phase 3 (800)	Phase 2 (367)	Phase 2 (303)
Patients	Men or postmenopausal women	Postmenopausal women	Men or postmenopausal women	Men or women (any menopausal status)	Men or women (any menopausal status)
Prior CDK4/6i	**Required (100%)**	Permitted	Permitted	Permitted (79.7%)	Permitted (42%)
Allowed prior fulvestrant	**Yes**	No	No	Yes	Yes
Allowed prior chemotherapy in mBC	**Yes**	Yes	No	Yes	Yes
Data readout	**Positive (pivotal)**	Positive (nonpivotal)	Ongoing	Negative	Negative

1. Bidard FC, et al. *J Clin Oncol.* 2022;40(28):3246-3256. **2.** SERENA-2. ClinicalTrials.gov identifier: NCT04214288. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04214288 **3.** EMBER-3. Clinical Trials.gov identifier: NCT04975308. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04975308 **4.** AMEERA-3. ClinicalTrials.gov identifier: NCT04059484. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04059484 **5.** Tolaney SM, et al. *Ann Oncol*. 2022;33(Suppl 7):S88-S121; Abstr 212MO. **6.** Evaluate Vantage. Accessed July 20, 2022. https://www.evaluate.com/vantage/articles/news/trial-results/roche-has-rare-breast-cancer-setback **7.** acelERA ClinicalTrials.gov identifier: NCT04576455. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04576455 **8.** Martin M, et al. *J Clin Oncol*. 2021;39(15):Abstr TPS1100. **9.** Martin Jimenez M, et al. *Ann Oncol.* 2022;33(Suppl 7):S88-S121; Abstr 211MO.

Study Design

Inclusion Criteria
- Men and postmenopausal women with advanced/mBC
- ER+,[a] HER2-
- Progressed or relapsed on or after 1 or 2 lines of ET for advanced disease, one of which was given in combination with a CDK4/6i
- ≤1 line of chemotherapy for advanced disease
- ECOG PS 0 or 1



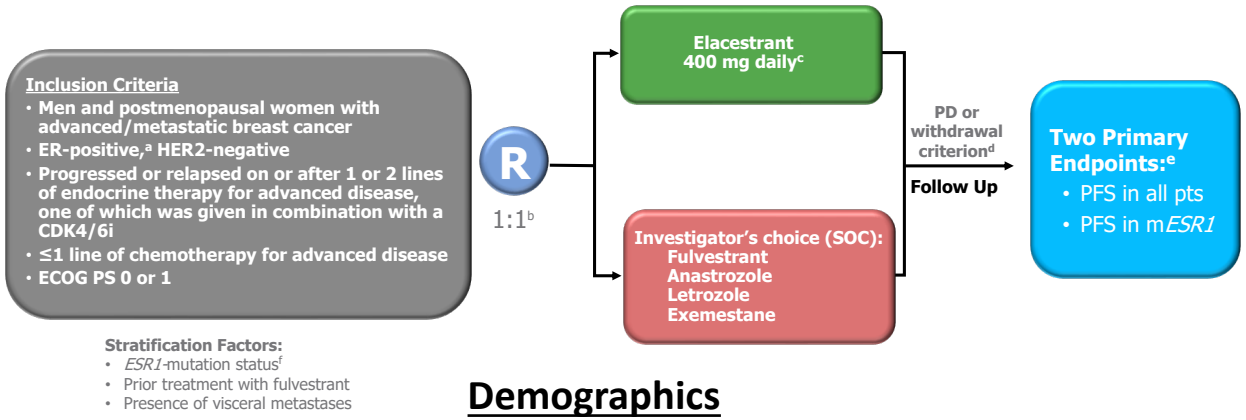
Stratification factors:
- *ESR1* mutation status[e]
- Prior treatment with fulvestrant
- Presence of visceral metastases

SOC guidance recommended use of a different ET than previously received (ie, fulvestrant recommended for patients who *had not* previously received fulvestrant, and selection of AI was based on prior AI therapy)

[a] Documentation of ER+ tumor with ≥1% staining by immunohistochemistry (local laboratory). [b] Recruitment from February 2019 to October 2020. [c] Protocol-defined dose reductions permitted. [d] Blinded independent central review. [e] *ESR1* mutation status was determined by cell-free circulating DNA analysis using Guardant360® CDx (Guardant Health, Redwood City, CA).

Bidard FC, et al. *J Clin Oncol*. 2022:40(28):3246-3256.

EMERALD Phase 3 Trial: Elacestrant vs SOC ET



Demographics

- ~70% visceral mets
- ~40% 2 lines prior ET for MBC
- ~24% one line of chemotherapy
- 100% prior CDK4/6i

Conclusions

- Hazard ratios are relatively similar in pts who received >6 months prior CDK4/6i or longer
- Pts with endocrine sensitive disease had remarkable PFS with elacestrant alone
- Benefit was more marked in the ESR1 mutant population
- Next steps: combinations with targeted agents (ELEVATE)

Bardia, Bidard …… and **Kaklamani;** SABCS 2022

Slide credit: Hope Rugo, MD

PFS by Duration of CDK4/6i: All Patients

Duration on CDK4/6i in the metastatic setting

	At least 6 mo		At least 12 mo		At least 18 mo	
	Elacestrant (n=202)	SOC (n=205)	Elacestrant (n=150)	SOC (n=160)	Elacestrant (n=98)	SOC (n=119)
Median PFS Months (95% CI)	**2.79** (1.94 - 3.78)	**1.91** (1.87 - 2.14)	**3.78** (2.33 - 6.51)	**1.91** (1.87 - 3.58)	**5.45** (2.33 - 8.61)	**3.29** (1.87 - 3.71)
PFS rate at 6 months (95% CI)	34.40 (26.70 - 42.10)	19.88 (12.99 - 26.76)	41.56 (32.30 - 50.81)	21.72 (13.65 - 29.79)	44.72 (33.24 - 56.20)	25.12 (15.13 - 35.10)
PFS rate at 12 months (95% CI)	21.00 (13.57 - 28.43)	6.42 (0.75 - 12.09)	25.64 (16.49 - 34.80)	7.38 (0.82 - 13.94)	26.70 (15.61 - 37.80)	8.23 (0.00 - 17.07)
PFS rate at 18 months (95% CI)	16.24 (8.75 - 23.74)	3.21 (0.00 - 8.48)	19.34 (9.98 - 28.70)	3.69 (0.00 - 9.77)	21.03 (9.82 - 32.23)	4.11 (0.00 - 11.33)
Hazard ratio (95% CI)	**0.688** (0.535 - 0.884)		**0.613** (0.453 - 0.828)		**0.703** (0.482 - 1.019)	

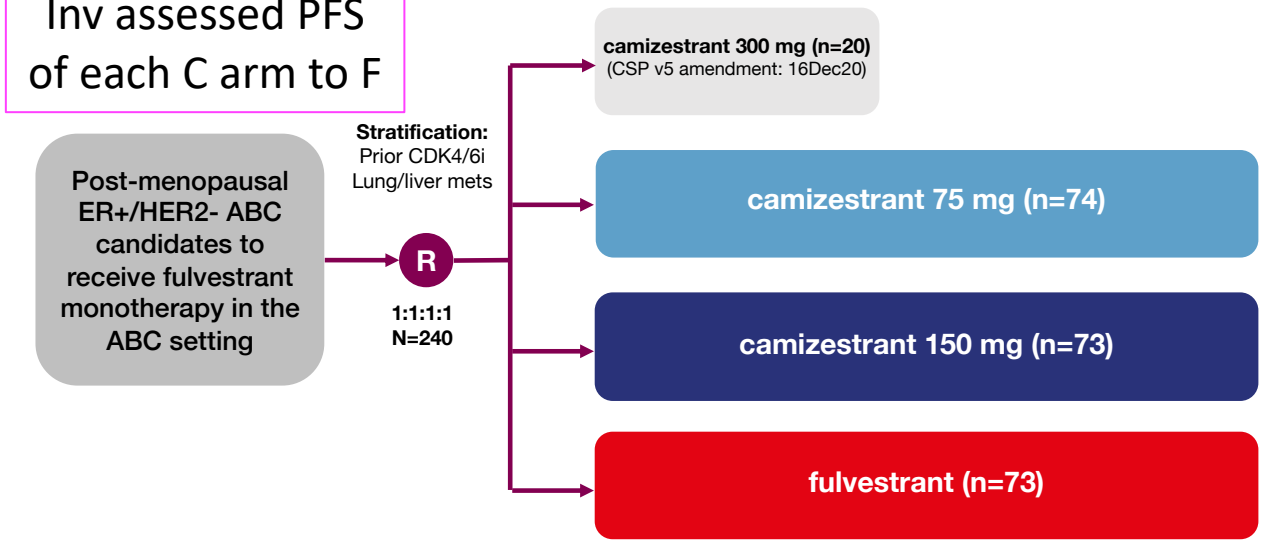
PFS by Duration of CDK4/6i: ESR1 mutant

Duration on CDK4/6i in the metastatic setting

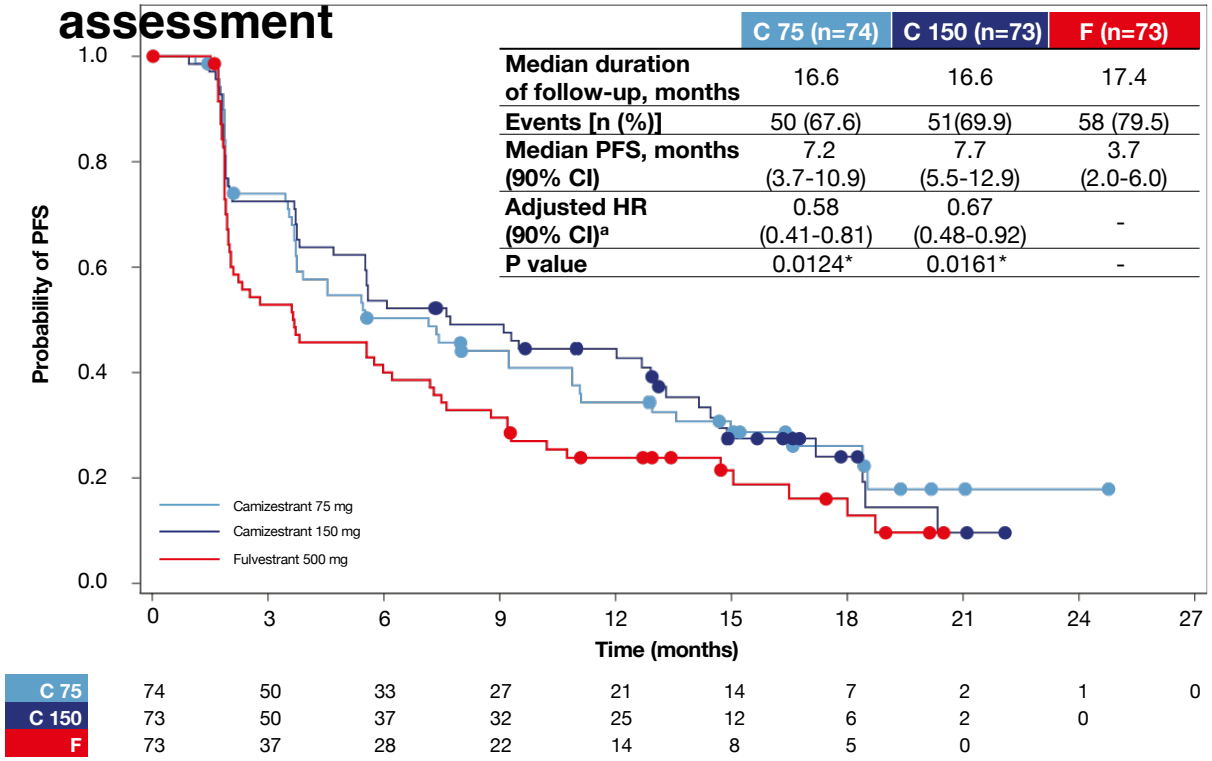
	At least 6 mo		At least 12 mo		At least 18 mo	
	Elacestrant (n=103)	SOC (n=102)	Elacestrant (n=78)	SOC (n=81)	Elacestrant (n=55)	SOC (n=56)
Median PFS Months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 6 months (95% CI)	42.43 (31.15 - 53.71)	19.15 (9.95 - 28.35)	55.81 (42.69 - 68.94)	22.66 (11.63 - 33.69)	58.57 (43.02 - 74.12)	27.06 (13.05 - 41.07)
PFS rate at 12 months (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
PFS rate at 18 months (95% CI)	20.70 (9.77 - 31.63)	0.00 (. - .)	28.49 (14.08 - 42.89)	0.00 (. - .)	30.68 (13.94 - 47.42)	0.00 (. - .)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)		**0.410** (0.262 - 0.634)		**0.466** (0.270 - 0.791)	

SERENA-2 Phase 2 Trial: Camizestrant plus Fulvestrant

Primary endpt: Inv assessed PFS of each C arm to F



Primary endpoint: PFS by investigator assessment



	C 75 (n=74)	C 150 (n=73)	F (n=73)
Median duration of follow-up, months	16.6	16.6	17.4
Events [n (%)]	50 (67.6)	51(69.9)	58 (79.5)
Median PFS, months (90% CI)	7.2 (3.7-10.9)	7.7 (5.5-12.9)	3.7 (2.0-6.0)
Adjusted HR (90% CI)[a]	0.58 (0.41-0.81)	0.67 (0.48-0.92)	-
P value	0.0124*	0.0161*	-

*Statistically significant; [a]HRs adjusted for prior use of CDK4/6i and liver/lung metastases

Demographics

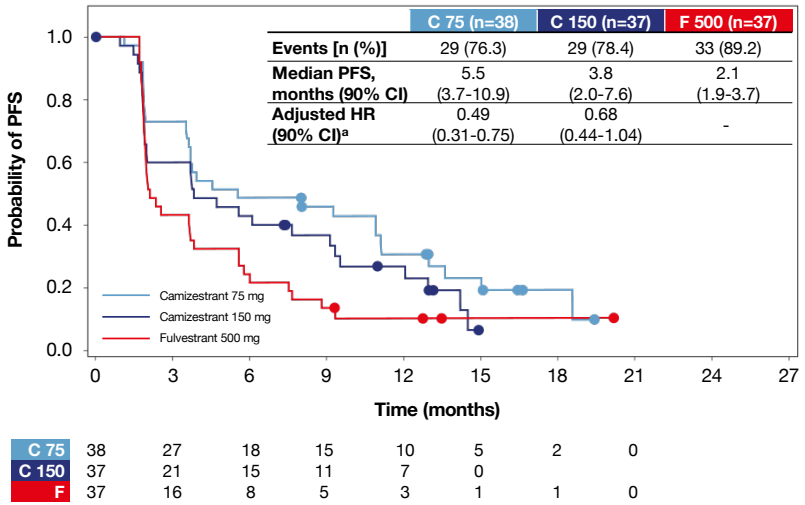
- 90-95% white
- Imbalance in liver (not visceral) mets: 31 v 41 vs 48%
- Imbalance in ESR1m: 30 v 36 v 48%
- 77% one line ET, 63% prior AI; 50% prior CDK4/6i
- Prior chemo for MBC: 22 v 12 v 26%

PFS by BICR: Significant discordance with inv PFS for 150 mg

	C 75 (n=74)	C 150 (n=73)	F (n=73)
Events [n (%)]	39 (52.7)	33 (45.2)	53 (72.6)
Median PFS, months (90% CI)	7.4 (4.5-10.9)	12.7 (9.3-18.4)	3.7 (2.0-3.8)
Adjusted HR (90% CI)[a]	0.56 (0.39-0.80)	0.47 (0.33-0.68)	-
P value	0.0079*	0.0004*	-

Oliveira et al, SABCS 2022

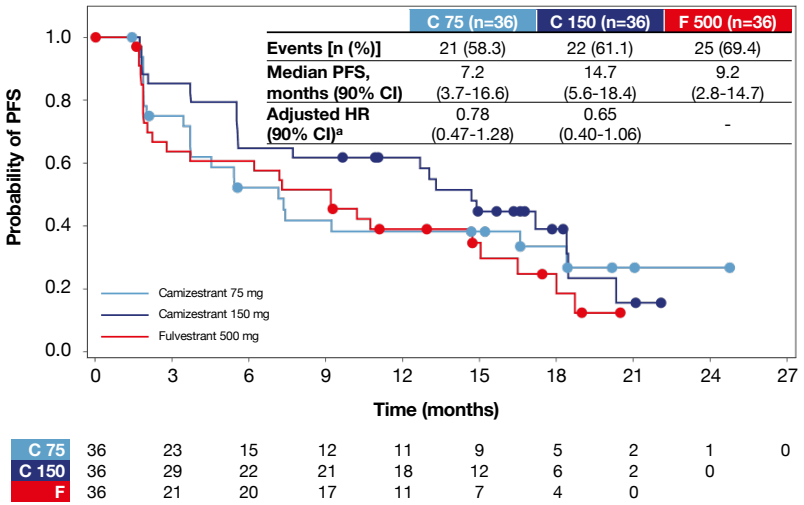
Prior CDK4/6i



	C 75 (n=38)	C 150 (n=37)	F 500 (n=37)
Events [n (%)]	29 (76.3)	29 (78.4)	33 (89.2)
Median PFS, months (90% CI)	5.5 (3.7-10.9)	3.8 (2.0-7.6)	2.1 (1.9-3.7)
Adjusted HR (90% CI)[a]	0.49 (0.31-0.75)	0.68 (0.44-1.04)	-

C 75	38	27	18	15	10	5	2	0	
C 150	37	21	15	11	7	0			
F	37	16	8	5	3	1	1	0	

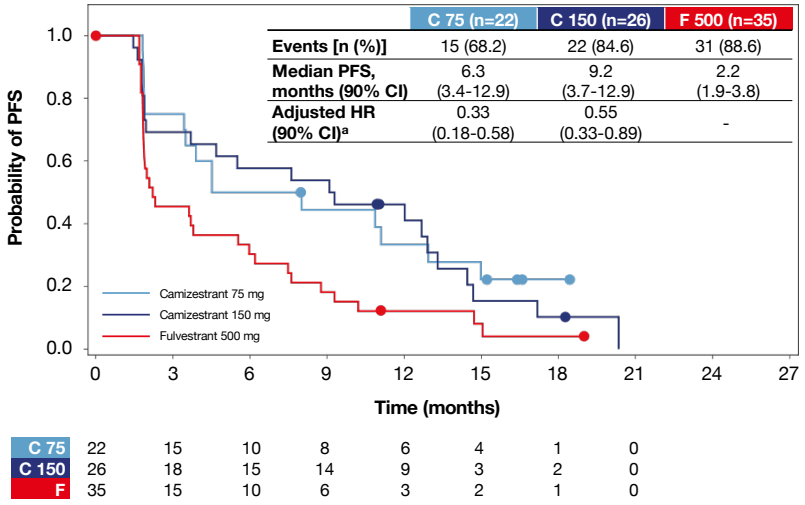
No prior CDK4/6i



	C 75 (n=36)	C 150 (n=36)	F 500 (n=36)
Events [n (%)]	21 (58.3)	22 (61.1)	25 (69.4)
Median PFS, months (90% CI)	7.2 (3.7-16.6)	14.7 (5.6-18.4)	9.2 (2.8-14.7)
Adjusted HR (90% CI)[a]	0.78 (0.47-1.28)	0.65 (0.40-1.06)	-

C 75	36	23	15	12	11	9	5	2	1	0
C 150	36	29	22	21	18	12	6	2	0	
F	36	21	20	17	11	7	4	0		

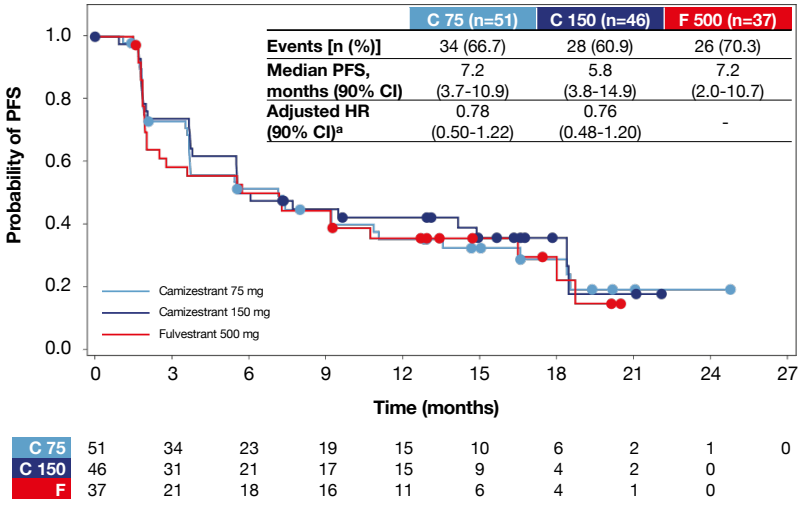
*ESR1*m detectable at baseline



	C 75 (n=22)	C 150 (n=26)	F 500 (n=35)
Events [n (%)]	15 (68.2)	22 (84.6)	31 (88.6)
Median PFS, months (90% CI)	6.3 (3.4-12.9)	9.2 (3.7-12.9)	2.2 (1.9-3.8)
Adjusted HR (90% CI)[a]	0.33 (0.18-0.58)	0.55 (0.33-0.89)	-

C 75	22	15	10	8	6	4	1	0
C 150	26	18	15	14	9	3	2	0
F	35	15	10	6	3	2	1	0

*ESR1*m not detectable at baseline



	C 75 (n=51)	C 150 (n=46)	F 500 (n=37)
Events [n (%)]	34 (66.7)	28 (60.9)	26 (70.3)
Median PFS, months (90% CI)	7.2 (3.7-10.9)	5.8 (3.8-14.9)	7.2 (2.0-10.7)
Adjusted HR (90% CI)[a]	0.78 (0.50-1.22)	0.76 (0.48-1.20)	-

C 75	51	34	23	19	15	10	6	2	1	0
C 150	46	31	21	17	15	9	4	2	0	
F	37	21	18	16	11	6	4	1	0	

Liver and/or lung mets

YES	C 75 (n=43)	C 150 (n=43)	F 500 (n=43)
Events [n (%)]	31 (72.1)	32 (74.4)	39 (90.7)
Median PFS, months (90% CI)	7.2 (3.6-11.1)	5.6 (3.7-9.1)	2.0 (1.9-3.6)
Adjusted HR (90% CI)[a]	0.43 (0.28-0.65)	0.55 (0.37-0.82)	-

NO	C 75 (n=31)	C 150 (n=30)	F 500 (n=30)
Events [n (%)]	19 (61.3)	19 (63.3)	19 (63.3)
Median PFS, months (90% CI)	5.5 (3.7-15.0)	14.5 (5.6-17.2)	9.2 (3.7-18.7)
Adjusted HR (90% CI)[a]	0.99 (0.57-1.69)	0.91 (0.53-1.56)	-

Biomarkers

- Camizestrant reduced ESR1 ctDNA to near zero by C2D1

Safety

- Very low rate discontinuation
- Interruption TRAEs ~med 7 days: ~10%
- Very low rate of grade 3 AEs
- All grade AEs (low-high dose):
  - Photopsia: 12-25%
  - Sinus bradycardia: 5-26%
  - More fatigue, arthralgia, AST/ALT elevation at higher dose

• Conclusion

- Met its primary endpoint
- No comment about dosing or imbalance in specific factors
  - Ph 3 trials ongoing
  - Dose: 75 mg

Oliveira et al, SABCS 2022

SERDs as monotherapy in the 2nd/3rd line setting post CDK4/6i

	EMERALD (PH III)	SERENA-2 (PH II)	
Oral SERD	Elacestrant	Camizestrant	
Standard arm	AI or FUL	Fulvestrant	
Pretreatment	1-2 ETX, 1 CTX	1 ETX, 1 CTX	
Prior CDK 4/6i / prior CTX (in ABC)	100% / 20-25%	51%/19%	
Fulvestrant (standard arm)	69% FUL by PC	100%	
Dose	400 mg	75 mg	150 mg
PFS mths	2.8 vs.1.9 mths 0.70 (0.55-0.88) **Δ 1.0 mths**	7.2 vs. 3.7 mths *0,58 (0.41-0.91)* **Δ 3.5 mths**	7.7 vs. 3.7 mths *0,67(0.48-0.92)* **Δ 4.0 mths**
PFS in mths **(prior CDK 4/6i)**	See above	5.5 vs. 2.1 mths *0,49 (0.31-0.75)* **Δ 3.4 mths**	3.8 vs. 2.1 mths *0,68 (0.44-1.04)* **Δ 1.7 mths**
PFS in mths (**ESR-1mutated**)	3.78 vs. 1.82 mths 0,55 (0.39-0.77) **Δ 2.0 mths**	6.3 vs. 2.2 mths *0,33 (0.18-0.58)* **Δ 4.1 mths**	9.2 vs. 2.2 mths *0,55 (0.33-0.89)* **Δ 7.0 mths**

Oliveira M et al. SABCS 2022,GS3-02; Bardia A et al. SABCS 2022,GS3-01

Imlunestrant: EMBER

Imlunestrant monotherapy: N = 114 (Jhaveri ASCO 2022)

Median 2 prior lines

51% prior fulvestrant

92% prior CDK4/6i

27% prior chemo

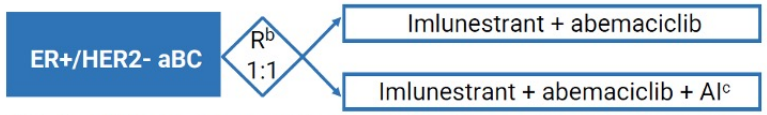
RP2D: 400mg daily

ORR 8%, CBR 42%; at 400g dose CBR 55%; PFS in 2L post CDK4/6i 6.5 months

Imlunestrant + Abemaciclib +/- AI: N = 85 (Jhaveri SABCS 2022)

Key Inclusion criteria:

- ER+, HER2- aBC
- ≤1 prior therapies for aBC but must not have received a prior CDK4/6 inhibitor
- Demonstrated prior sensitivity to endocrine therapy[a] or have untreated de novo aBC



[a] Defined as CR/PR or SD ≥ 24 weeks on ET in advanced setting OR ≥ 24 months on ET in adjuvant setting
[b] Stratified by menopausal status and visceral metastases. Randomization was for enrollment purposes and not for any formal comparison between cohorts.
[c] Physician's Choice AI (Anastrozole, Exemestane, or Letrozole) per label dose and schedule

Table 3. Efficacy parameters in evaluable patients

	Imlunestrant + abemaciclib N=42	Imlunestrant + abemaciclib + AI N=43	Total N=85
ORR, n/N (%)	9/28 (32)	20/34 (59)	29/62 (47)
Median TTR, months (min-max)	3.7 (1.6-10.9)	3.7 (1.7-7.1)	3.7 (1.6-10.9)
CBR, n/N (%)	30/42 (71)	34/43 (79)	64/85 (75)
12-month PFS, %	80	80	80

Safety profile (diarrhea, nausea, fatigue, neutropenia) compared favorably to fulvestrant + Abemaciclib in MONARCH 2

No drug-drug PK interactions

Additional Phase III SERD Trials for MBC: Examples

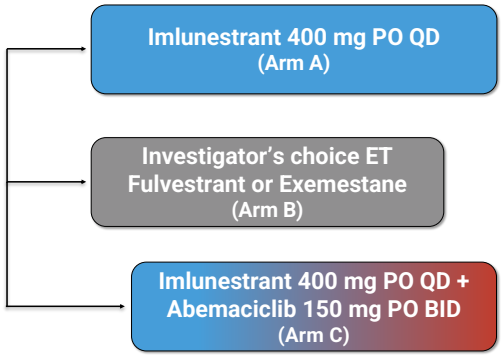
EMBER-3

1:1:1 Randomization
N = ~860

ER+, HER2-, Advanced Breast Cancer

- Relapsed on (neo) adjuvant/within 1 year of adjuvant AI, alone or in combination with a CDK4/6 inhibitor
  OR
- Progressed on 1L AI, alone or in combination with a CDK4/6 inhibitor
- Prior CDK4/6i treatment is expected if approved and reimbursed

Stratified for:
- Prior CDK4 & 6 inhibitor therapy
- Presence of visceral metastases
- Region

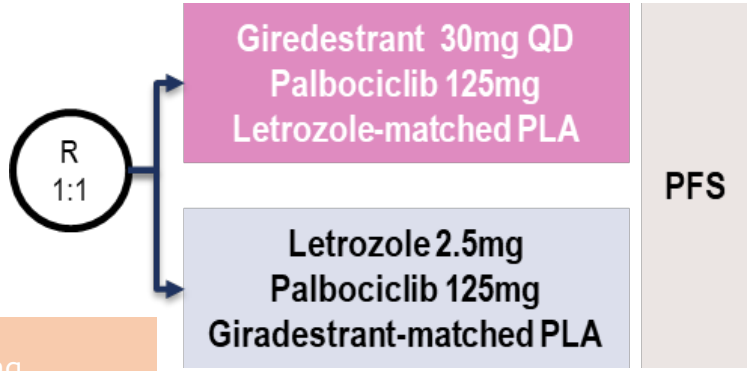


Primary Objective:
- Investigator-assessed PFS for A vs B
- Investigator-assessed PFS for A vs B in the *ESR1*-mutation detected population
- Investigator-assessed PFS for C vs A (gated, i.e. only tested if A vs B is stat sig)

Secondary Objectives:
- OS (gated), PFS by BICR, ORR, CBR, DoR, PRO's

persevERA

N=978
- ER+/HER2- LA/ABC
- No prior systemic tx for ABC

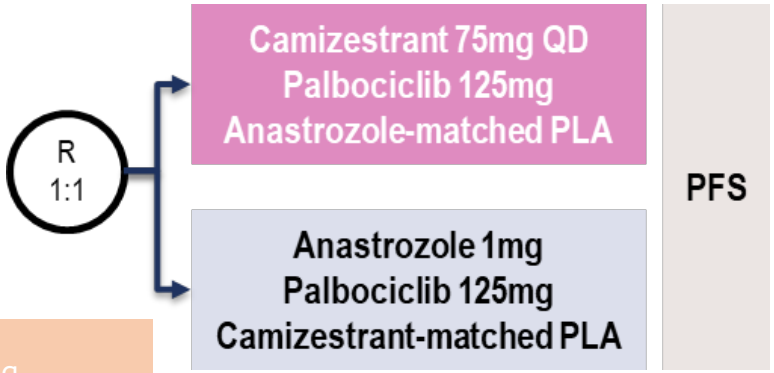


Recruiting

NCT04546009

SERENA-4

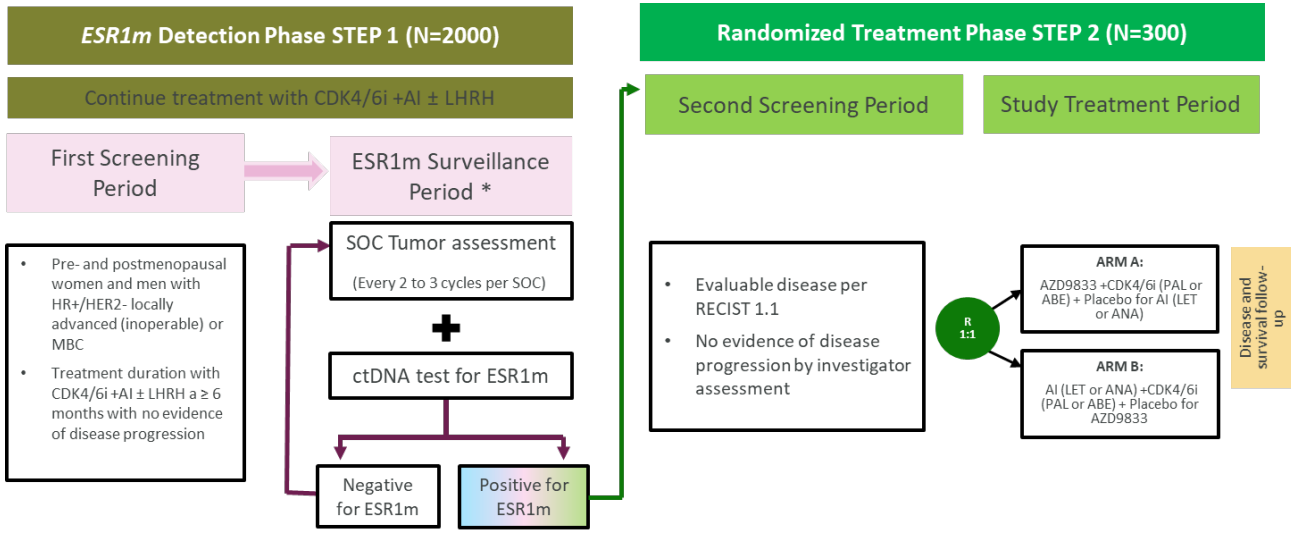
N=1342
- ER+/HER2- LA/ABC
- No prior systemic tx for ABC



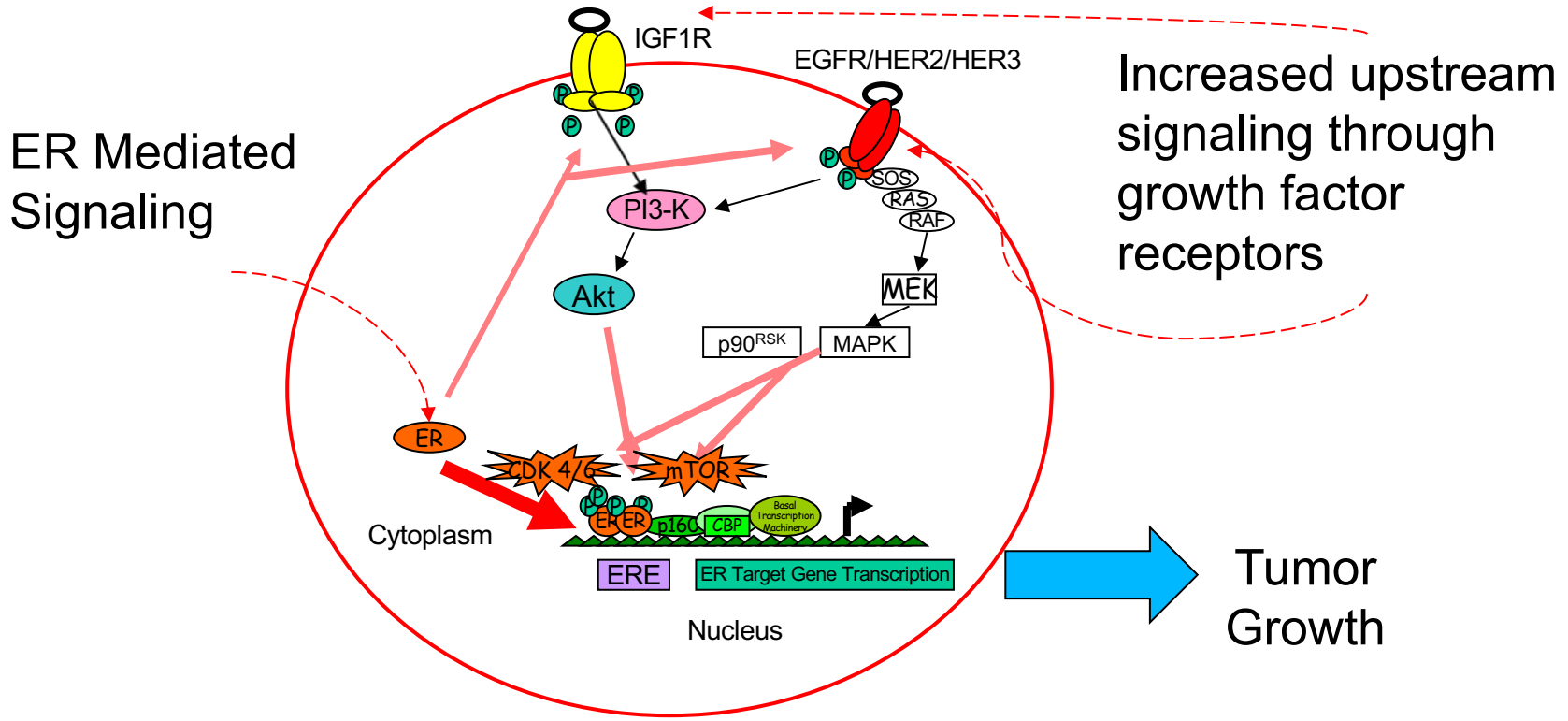
Recruiting

NCT04711252

SERENA-6



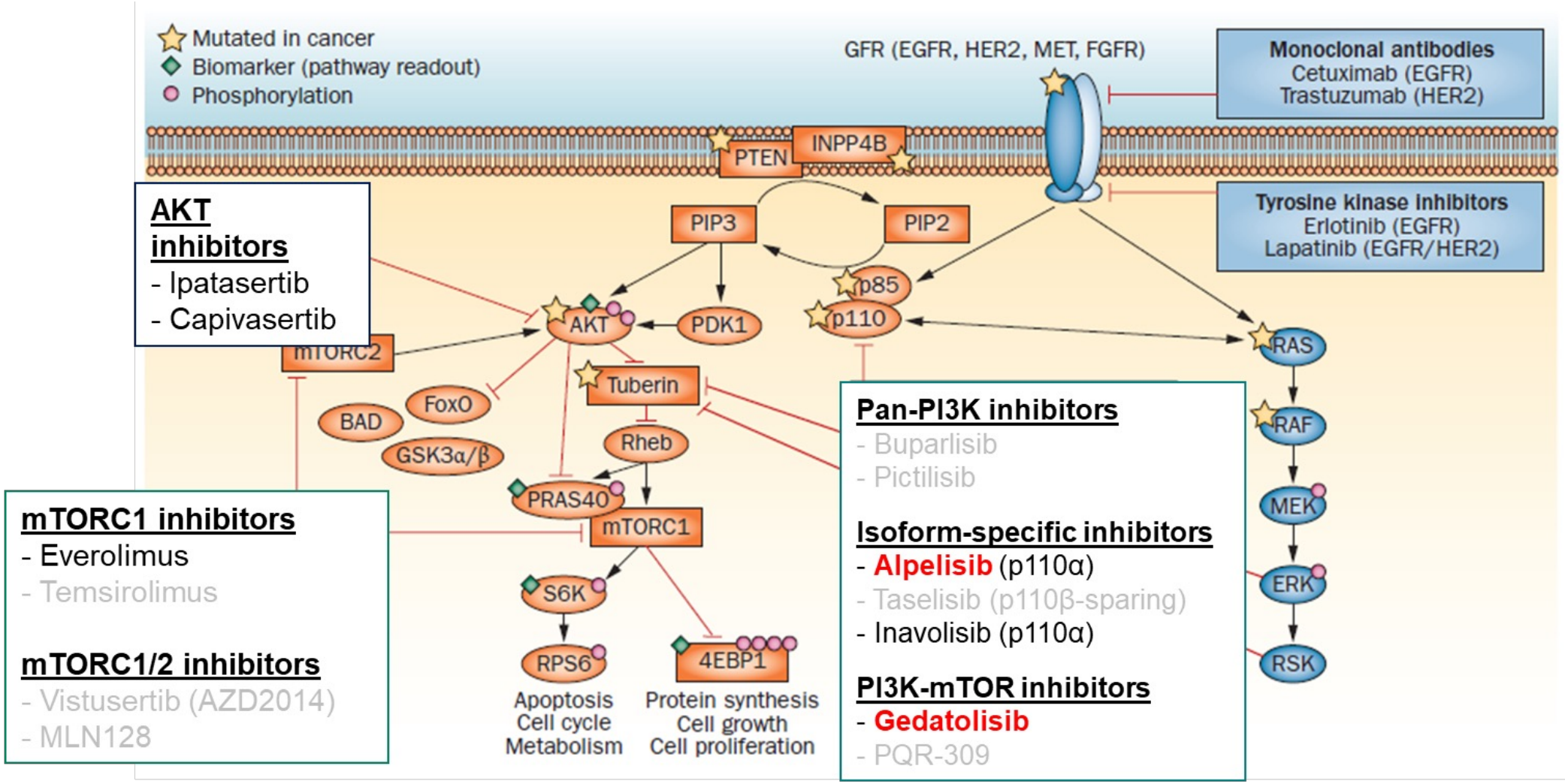
Optimal Biological Effect Does Not Guarantee Clinical Efficacy



Endocrine Therapy with 100% ER Pathway Inhibition would have limited impact on a tumor that is ER-pathway independent

Adapted from Johnston ST. J Natl Cancer Inst. 2015.

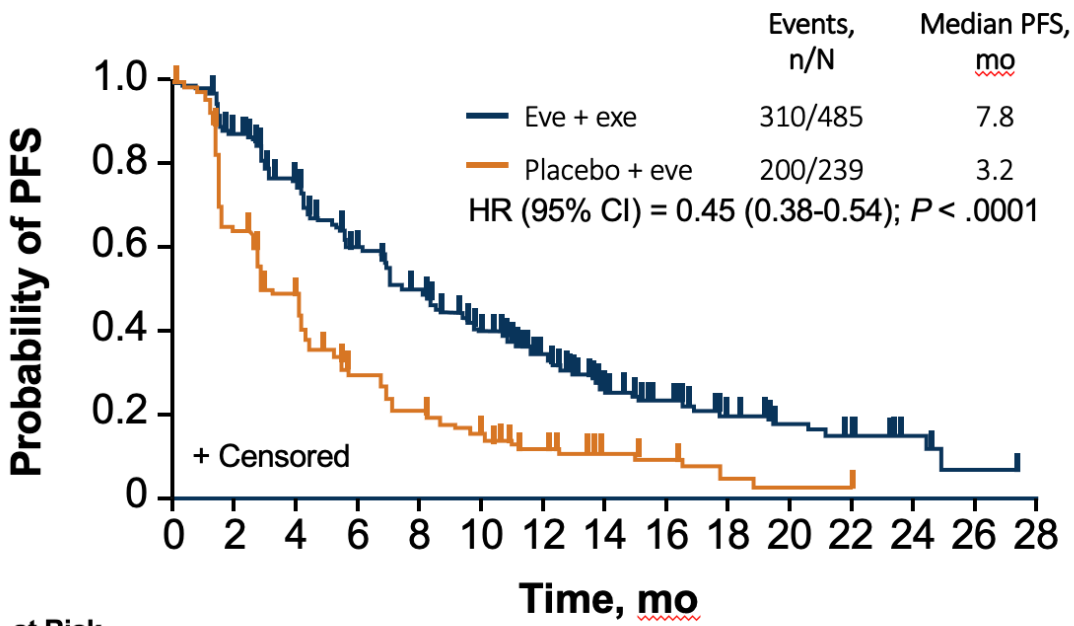
PI3K Pathway Inhibitors



Adapted from Rodon J, et al. *Nat Rev Clin Oncol*. 2013;10:143-153.

BOLERO-2 and PrE0102 Trial : Improved PFS With mTOR Inhibition

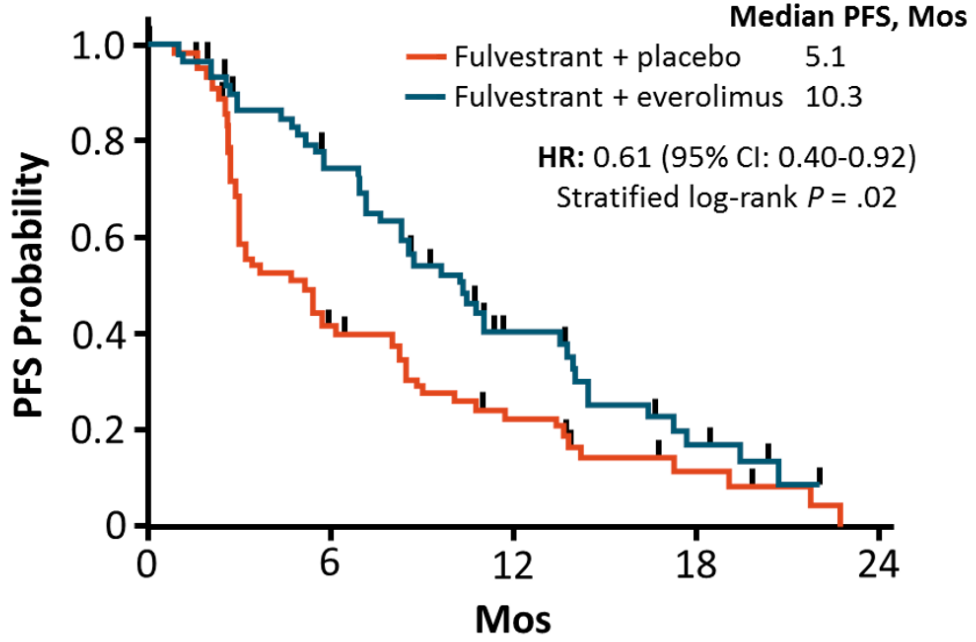
Local Assessment



No. at Risk

Eve + exe	485	394	318	236	194	147	99	57	42	23	13	10	4	1	0
Placebo + eve	239	146	103	61	42	27	17	9	6	2	1	1	0	0	0

Investigator-Assessed PFS



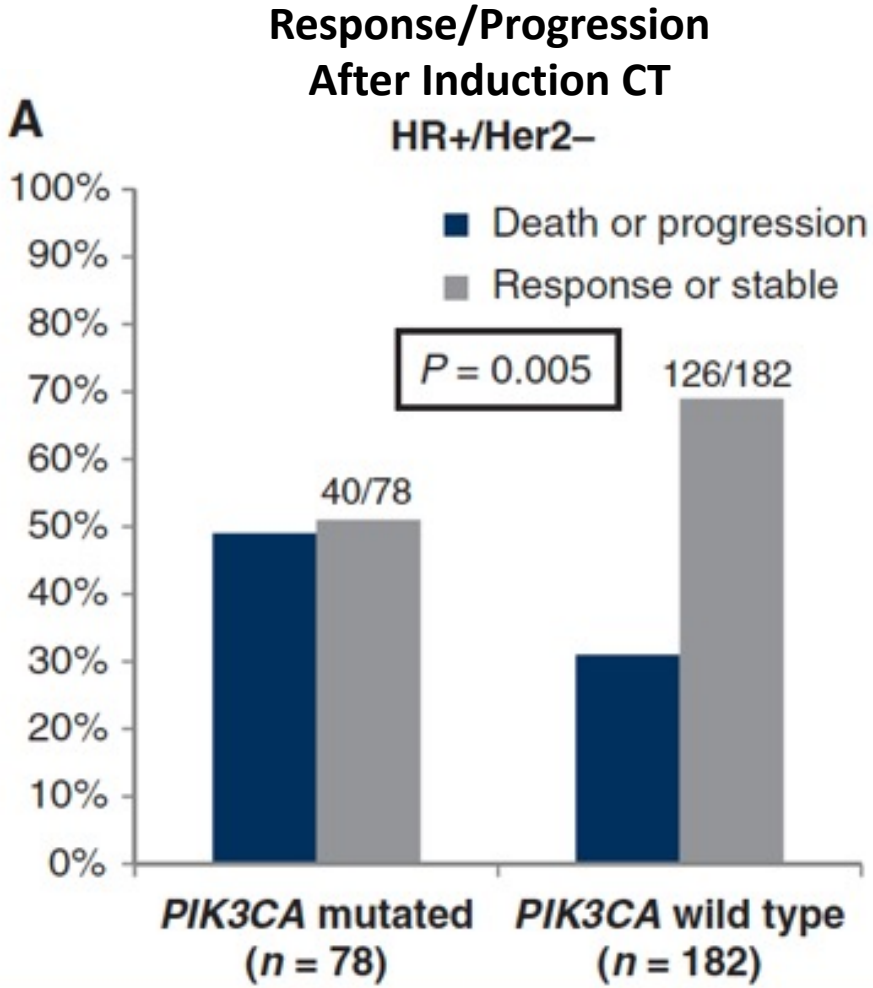
No. at Risk

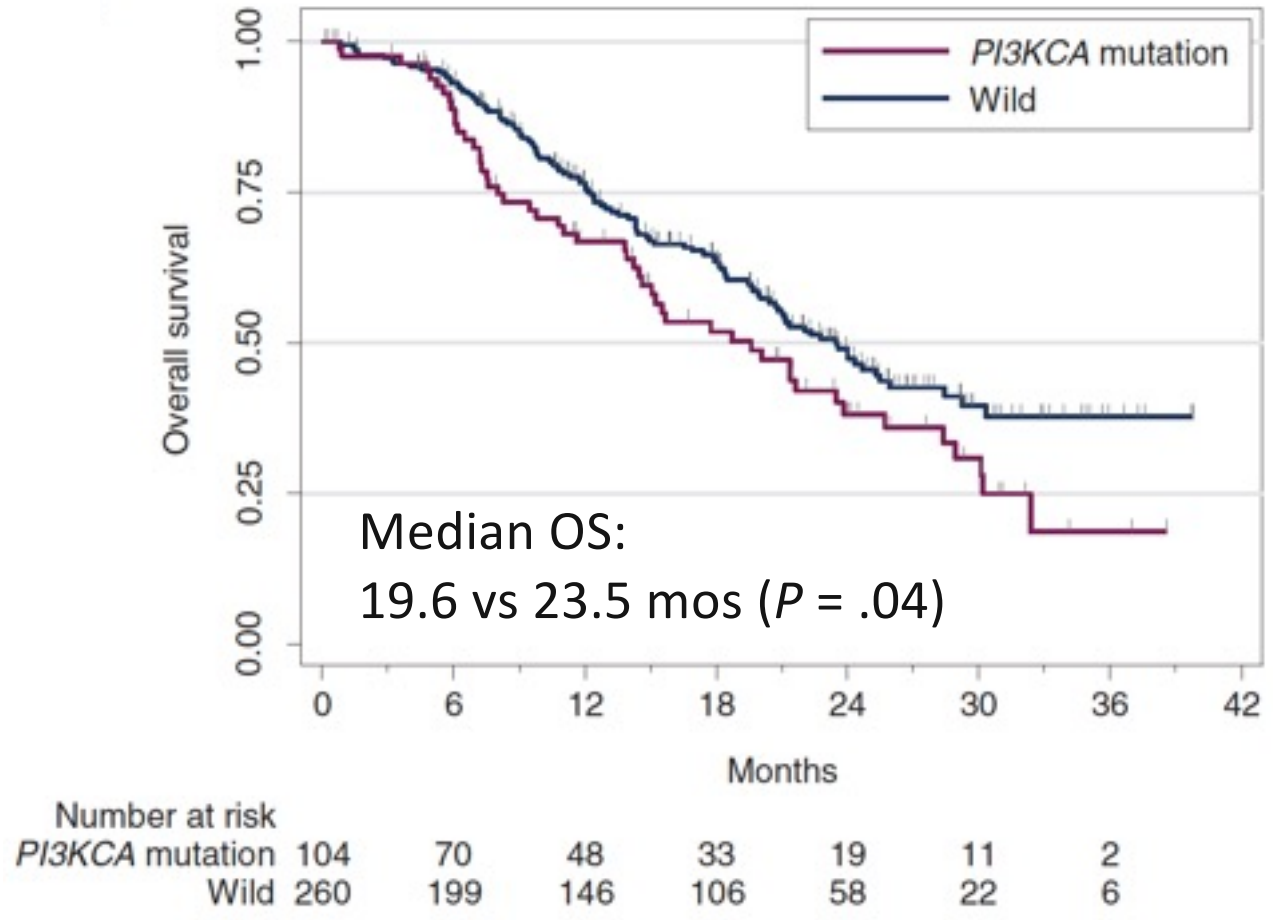
	65	25	12	4	0
	66	41	17	6	1

- Improved PFS with mTOR inhibition regardless of *PIK3CA* mutation
- Similar results with tamoxifen + everolimus

PIK3CA Mutations Associated With Poor Prognosis in SAFIR02

PIK3CA Mutations (*PIK3CA*m) Found in 28% of HR+/HER2- MBC (associated with older age and lower tumor grade, 93% had a single *PIK3CA* point mutation in exon 9 or exon 20)



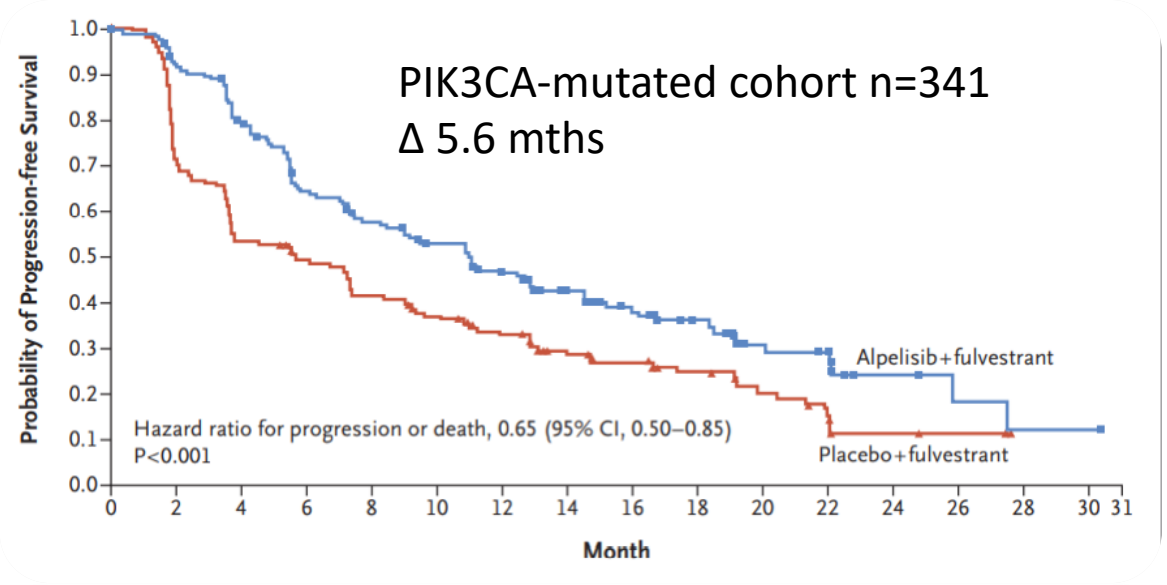


CT, chemotherapy.

Mosele F, et al. *Ann Oncol*. 2020;31:377-386.

Option for patients with *PIK3CA* mutations: Ful + Alpelisib

SOLAR-1(PH III): Fulvestrant +/- Alpelisib
(pts progressed on or after aromatase inhibitor)



- Numerical improvement in median OS of 7.9-month in the mutated cohort
- Discontinuation rate was 25% in FUL+ALP- arm versus 4% in the FUL-arm
- Most common side effects (Grade III): hyperglycemia (36%), rash (10%), diarrhea (7%)
- **6% had prior CDK 4/6*i***

Median PFS

11.0 months (ALP+FUL) versus 5.7 months (FUL); HR 0.65; 95% CI, 0.50 to 0.85; p<0.001

BYLieve (PhII, single arm, cohort A):

ALP + FULV showed clinical benefit after CDK 4/6*i* treatment: 50.4% 6-months PFS rate (median 7.3 mo)

Andre F et al NEJM 2019; Andre F et al. Ann Oncol 2021

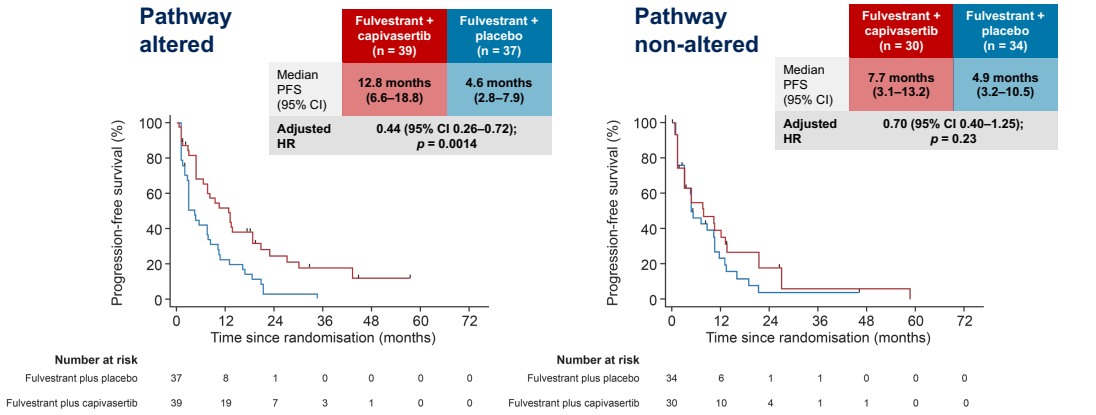
Inhibiting AKT

- AKT pathway activation occurs in many HR+/HER2– ABC through alterations in *PIK3CA, AKT1 and PTEN*
  - May also occur in cancers without these genetic alterations
  - AKT signalling implicated in development of ET resistance
- Capivasertib is a potent, selective inhibitor of all three AKT isoforms (AKT1/2/3)

Turner et al, SABCS 2022; Jones RH, et al. Lancet Oncol 2020; Howell et al, Lancet Oncology 2022

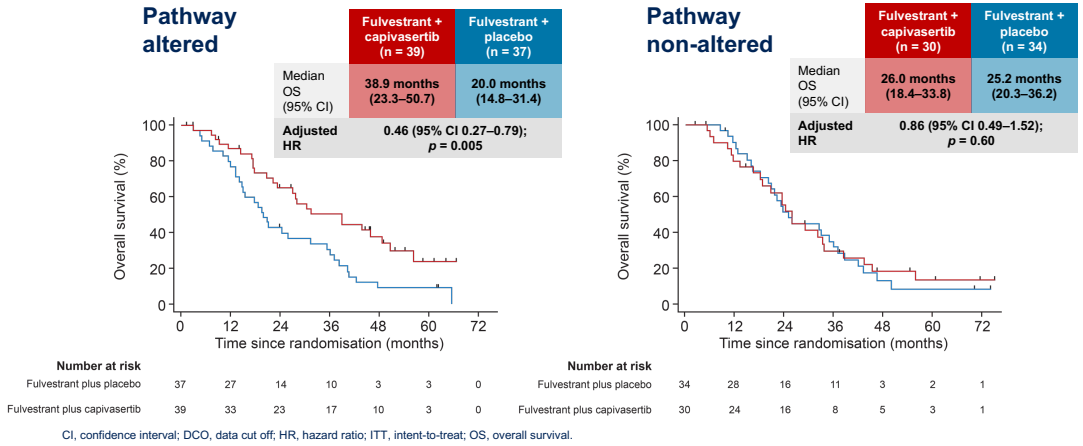
Phase II FAKTION Trial

- Adding Capi to Fulv in PM women with AI resistant HR+ MBC (no prior CDKi) improved PFS and OS, with most benefit in altered population



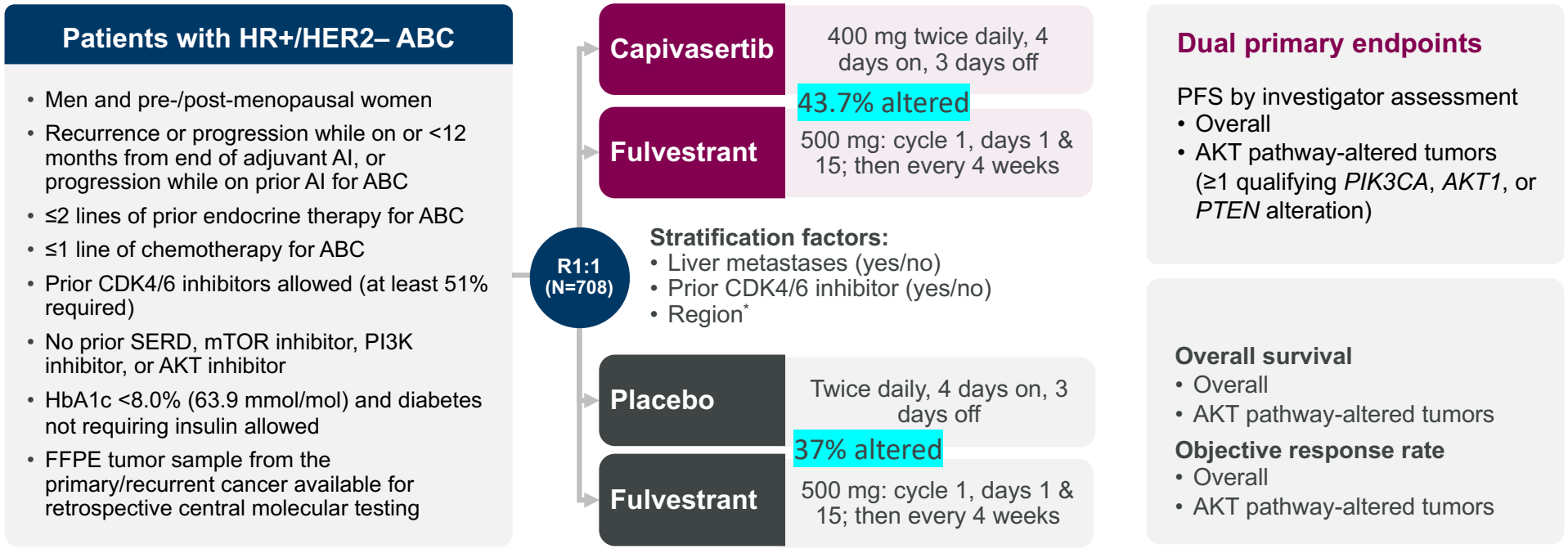
CI, confidence interval; DCO, data cut off; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival.

DCO Nov 2021



CI, confidence interval; DCO, data cut off; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival.

CAPItello-291: Phase III, randomized, double-blind, placebo-controlled study



Summary of Demographics

- Median age ~59
- Asian 26%, Black 1%
- Primary ET resistance ~38%
- Visceral mets ~68%
- One line of prior ET for MBC ~75%
- Prior CDK4/6i for MBC ~70%
- Chemotherapy for ABC ~18%

Turner et al, SABCS 2022

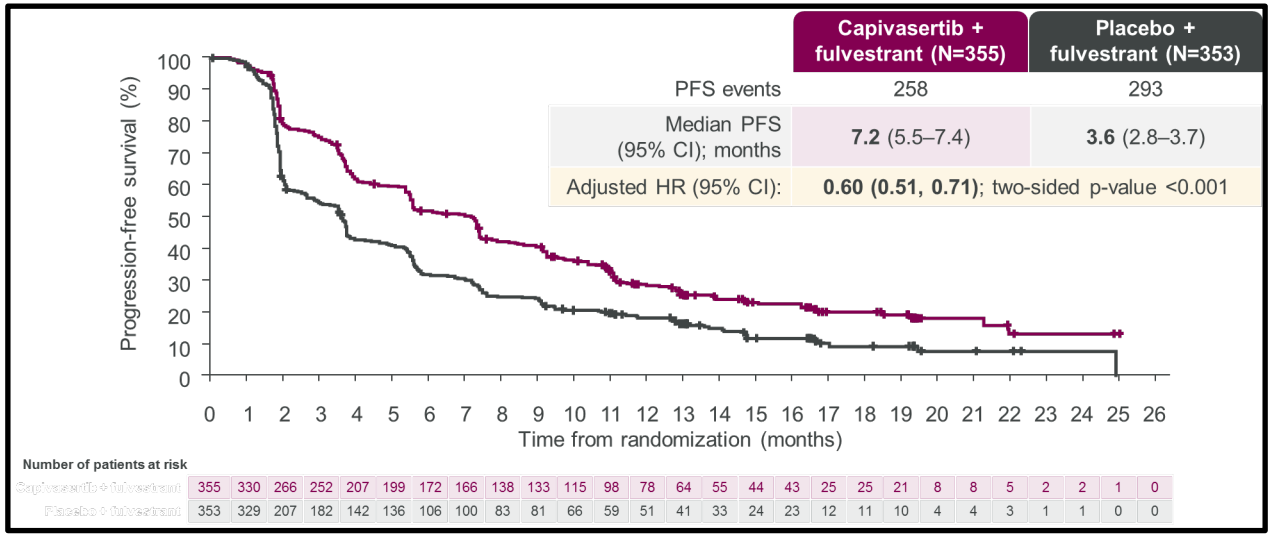
Phase 3 Capitello-291: AKT pathway alterations

Alteration; n (%)		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
Any AKT pathway alteration		**155 (43.7)**	**134 (38.0)**
PIK3CA	Any	116 (32.7)	103 (29.2)
	PIK3CA only	110 (31.0)	92 (26.1)
	PIK3CA and *AKT1*	2 (0.6)	2 (0.6)
	PIK3CA and *PTEN*	4 (1.1)	9 (2.5)
AKT1 only		18 (5.1)	15 (4.2)
PTEN only		21 (5.9)	16 (4.5)
Non-altered		**200 (56.3)**	**219 (62.0)**
AKT pathway alteration not detected		142 (40.0)	171 (48.4)
Unknown		58 (16.3)	48 (13.6)
No sample available		10 (2.8)	4 (1.1)
Preanalytical failure		39 (11.0)	34 (9.6)
Post analytical failure		9 (2.5)	10 (2.8)

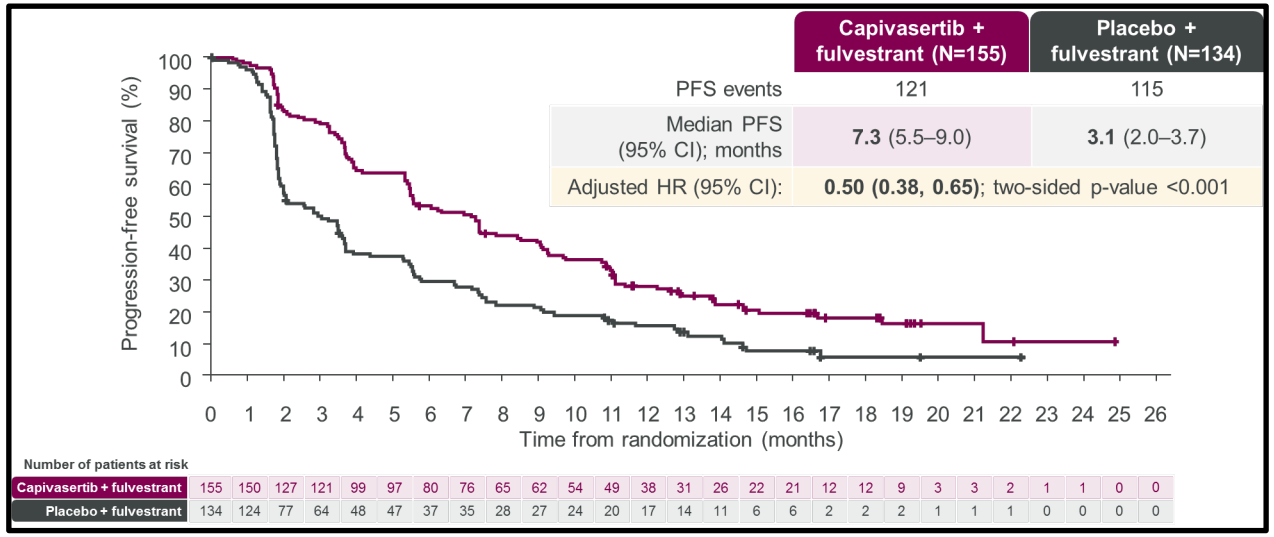
AKT pathway alteration status was determined centrally using next-generation sequencing in tumor tissue with the FoundationOne®CDx assay (and Burning Rock assay in China)

Turner et al SABCS 2022

Phase 3 Capitello-291: Dual-primary endpoint: Investigator-assessed PFS in the overall population and AKT pathway-altered population



Overall population



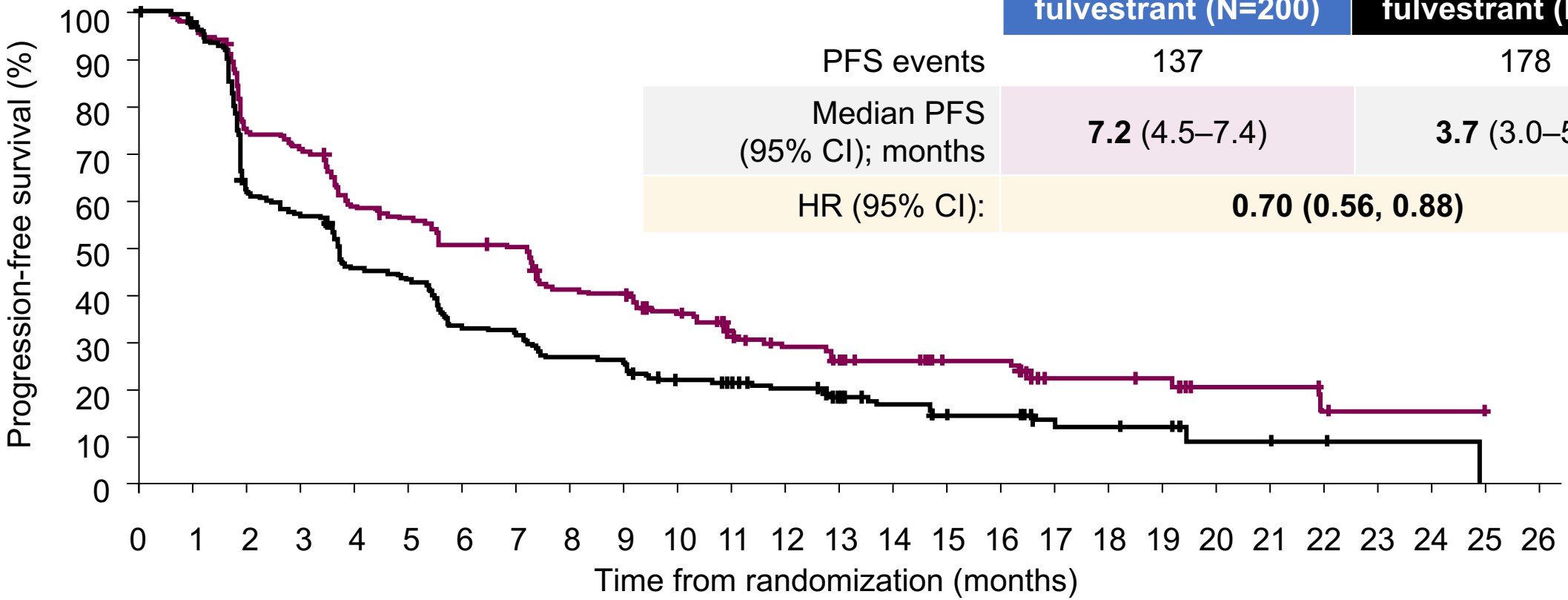
AKT pathway-altered population

13% discontinuation, 20% dose reduction; most common AE: diarrhea , rash, nausea, fatigue
Diarrhea grade 3 : 9.3%
Rash grade 3 12%
Hyperglycemia grade 3 2.3%

Turner et al SABCS 2022

Phase 3 Capitello-291: Exploratory analysis: Investigator-assessed PFS in the non-altered population (including unknown†)

	Capivasertib + fulvestrant (N=200)	Placebo + fulvestrant (N=219)
PFS events	137	178
Median PFS (95% CI); months	**7.2** (4.5–7.4)	**3.7** (3.0–5.0)
HR (95% CI):	**0.70 (0.56, 0.88)**	



Number of patients at risk

Capivasertib + fulvestrant	200	180	139	131	108	102	92	90	73	71	61	49	40	33	29	22	22	13	13	12	5	5	3	1	1	1	0
Placebo + fulvestrant	219	205	130	118	94	89	69	65	55	54	42	39	34	27	22	18	17	10	9	8	3	3	2	1	1	0	0

+ indicates a censored observation. †Patients with no valid NGS results. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and prior use of CDK4/6 inhibitor.

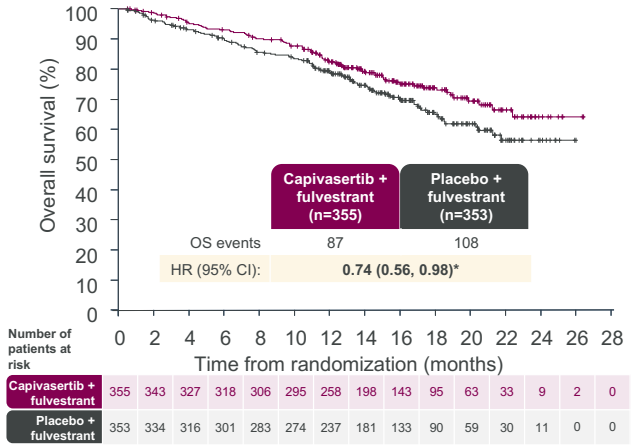
Turner et al SABCS 2022

Excluding unknowns:
HR 0.79 (95% CI 0.61, 1.02)

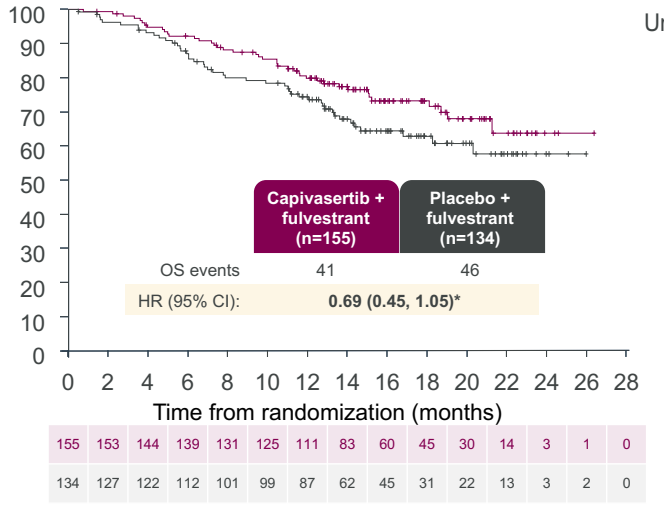
Overall Survival

- Overall survival immature at just 28% maturity
  - Less events in the Capi arm

Overall population

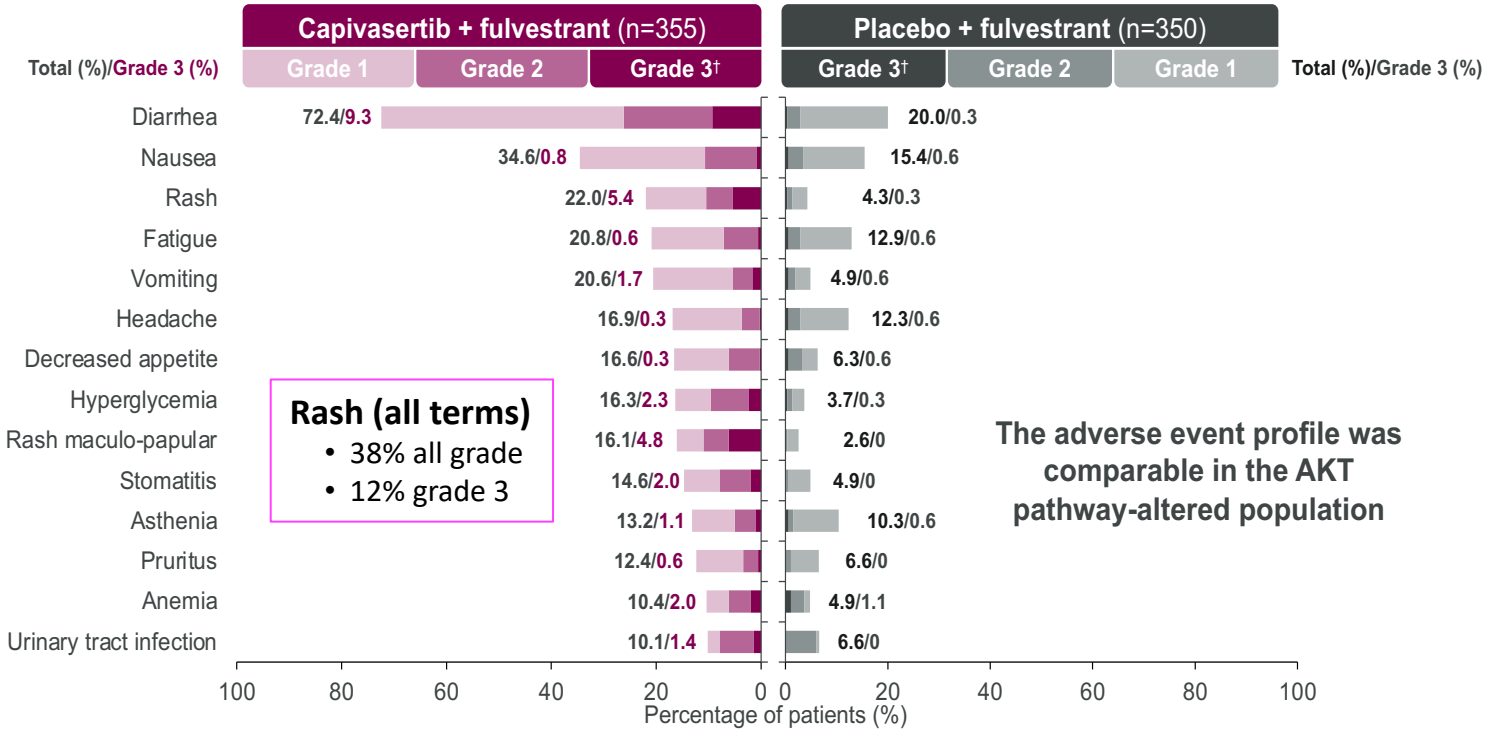


AKT pathway-altered population



Safety

Adverse events (>10% of patients) – overall population



Rash (all terms)
- 38% all grade
- 12% grade 3

The adverse event profile was comparable in the AKT pathway-altered population

Adverse events of any grade related to rash (group term including rash, rash macular, maculo-papular rash, rash papular and rash pruritic) were reported in 38.0% of the patients in the capivasertib + fulvestrant arm (grade ≥3 in 12.1%) and in 7.1% of those in the placebo + fulvestrant group (grade ≥3 in 0.3%). †All events shown were Grade 3 except one case of Grade 4 hyperglycemia in the capivasertib + fulvestrant arm.

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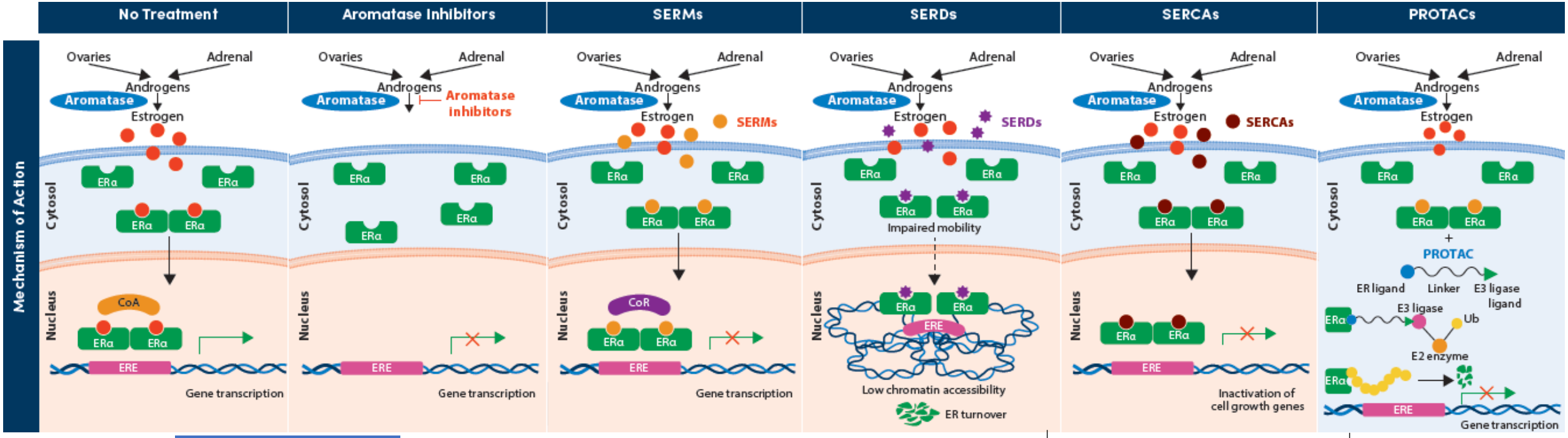
AEs leading to:

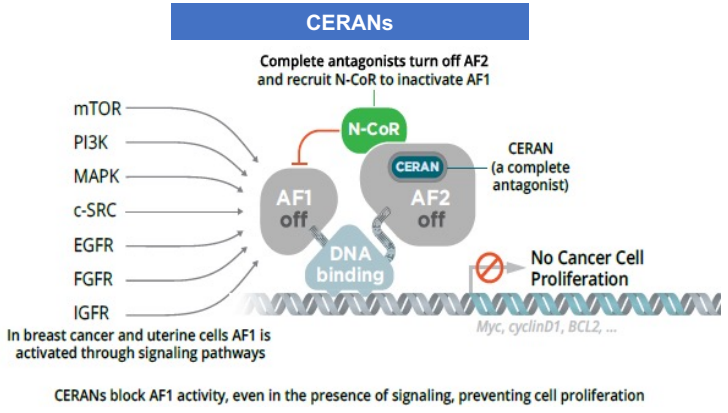
- Discontinuation capi/pla: 9.3 vs 0.6%
- Interruption capi/pla: 34.9 vs 10.3%
- Dose reduction capi/pla: 19.7 vs 1.7%

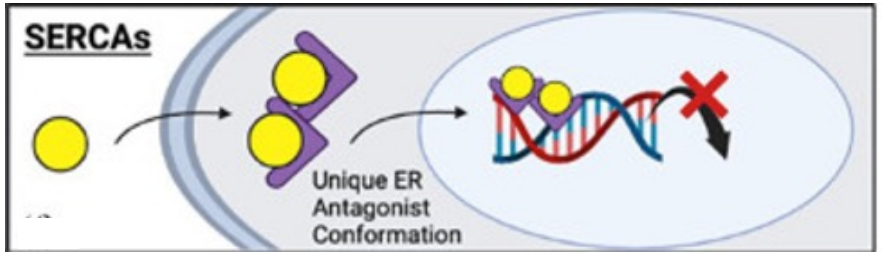
Turner et al, SABCS 2022

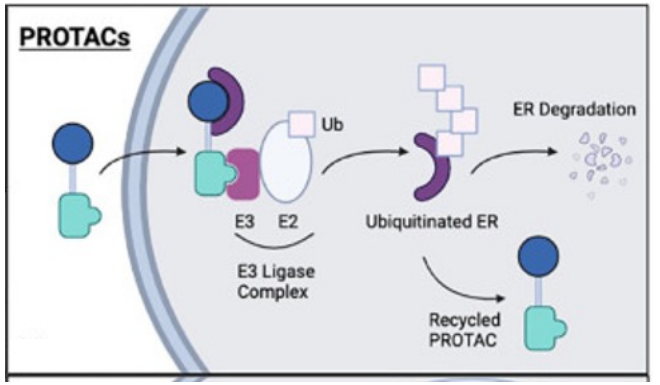
Other agents

Mechanism of Action of New Endocrine Agents Targeting the ER Domain









1. Hanker AB et al. *Cancer Cell.* 2020;37:496-513 2. Lloyd MR, et al. *Ther Adv Med Oncol* 2022, Vol. 14: 1–25

ARV-471: Efficacy in phase 1 trial

Patient population: N=71

- Median of 3 prior lines of prior therapy (any setting)
- 100% treated with CDK 4/6i
- 79% Fulvestrant
- 45% prior chemo

Results:

✓ No DLTs or G4 tx related AEs; MTD not reached

✓ Most tx related AEs were grade 1 or 2

✓ Responses in pts tx with prior CDK 4/6i, fulvestrant or SERD

CBR was 38%; 51% in *ESR1*m (2 cPR)

mPFS: 3.5m;5.5m in *ESR1m* (n=41)

Grade 1/2 nausea, fatigue, arthralgia, hot flush, AST increase

Median ER degradation was 69%
(range: 28%–95%)

- Ph 1b cohort ARV-471+palbociclib combination is ongoing
- Phase 3 VERITAC-2 trial planned

Hurvitz et al, SABCS 2022

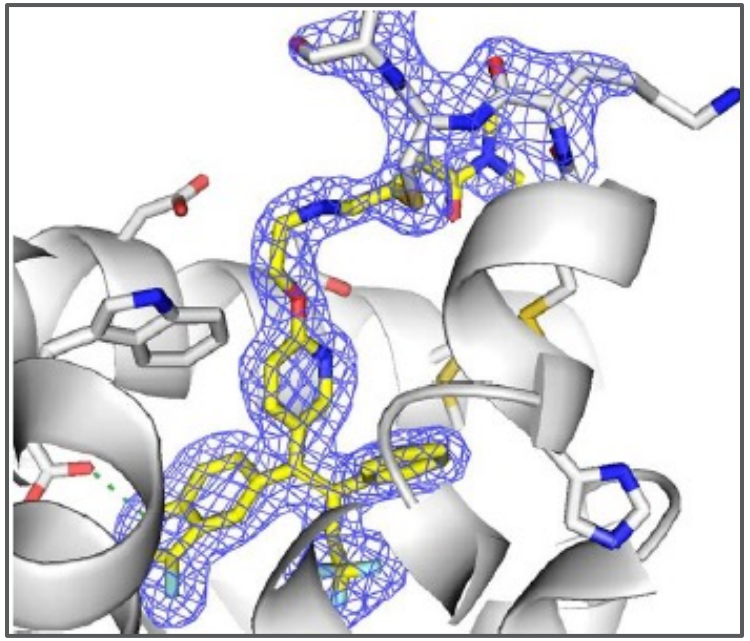
SERCA: Selective estrogen receptor antagonist

SERCAs

- target a unique cysteine in ER (position 530) not conserved in other nuclear hormone receptors
- equipotent in targeting of ERα WT and mutant in *in vitro PD assays*

H3B-6545 (H3 Biomedicine)

- first-in-class SERCA that binds ERα irreversibly and enforces a novel antagonist conformation without degrading ERα
- appears to have increased efficacy in combination in palbociclib

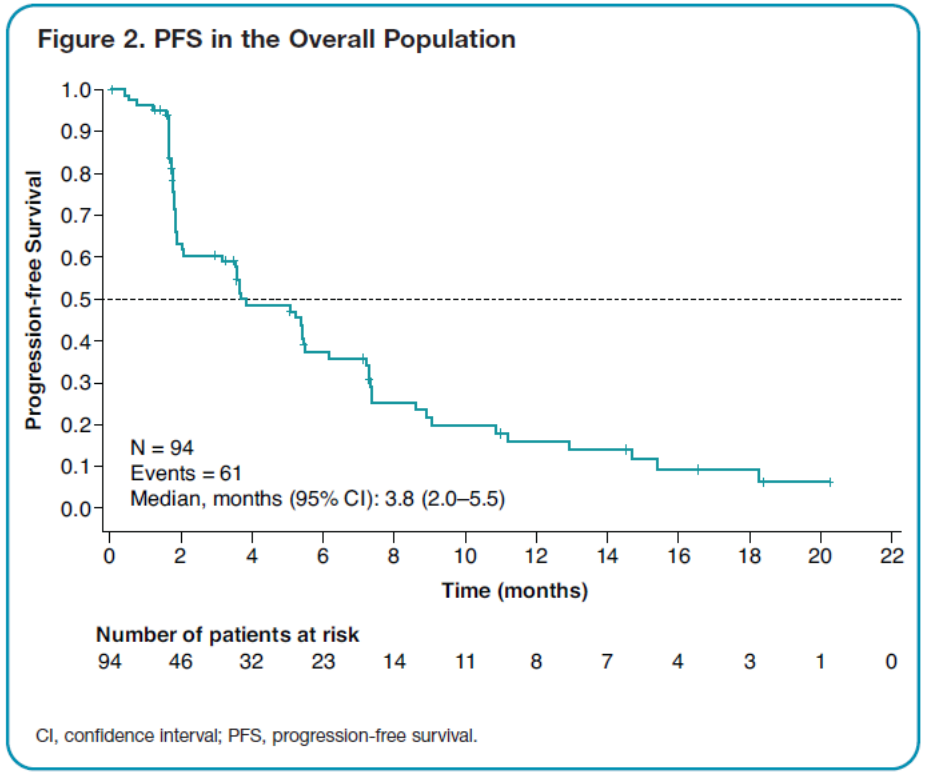


X-ray structure of H3B-6545 demonstrating covalent engagement with C530 of ERαY537S mutant receptor

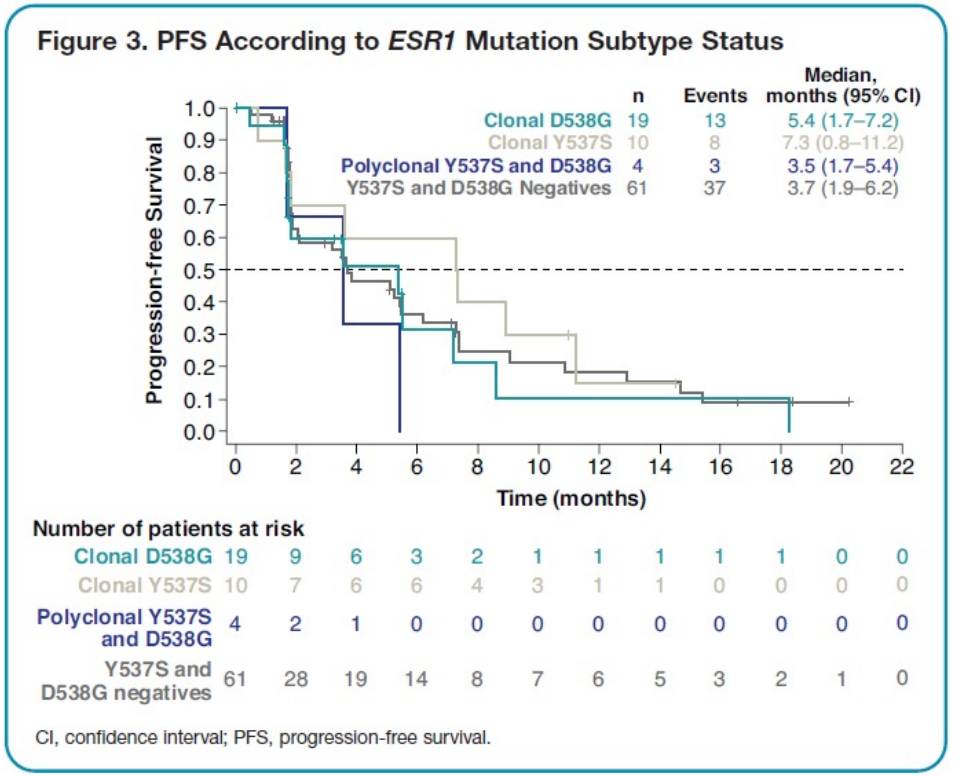
H3B-6545 in ER+/HER2- MBC (ph 1 data)

H3B-6545 (450mg) in heavily pretreated HR+/HER2- MBC (N=94)

- Median of 3 prior lines of therapy (34% ≥ 4 lines of therapy)
- Prior CDK 4/6i: 87%
- Prior fulvestrant: 73%
- Prior chemo: 50%



@ErikaHamilton9



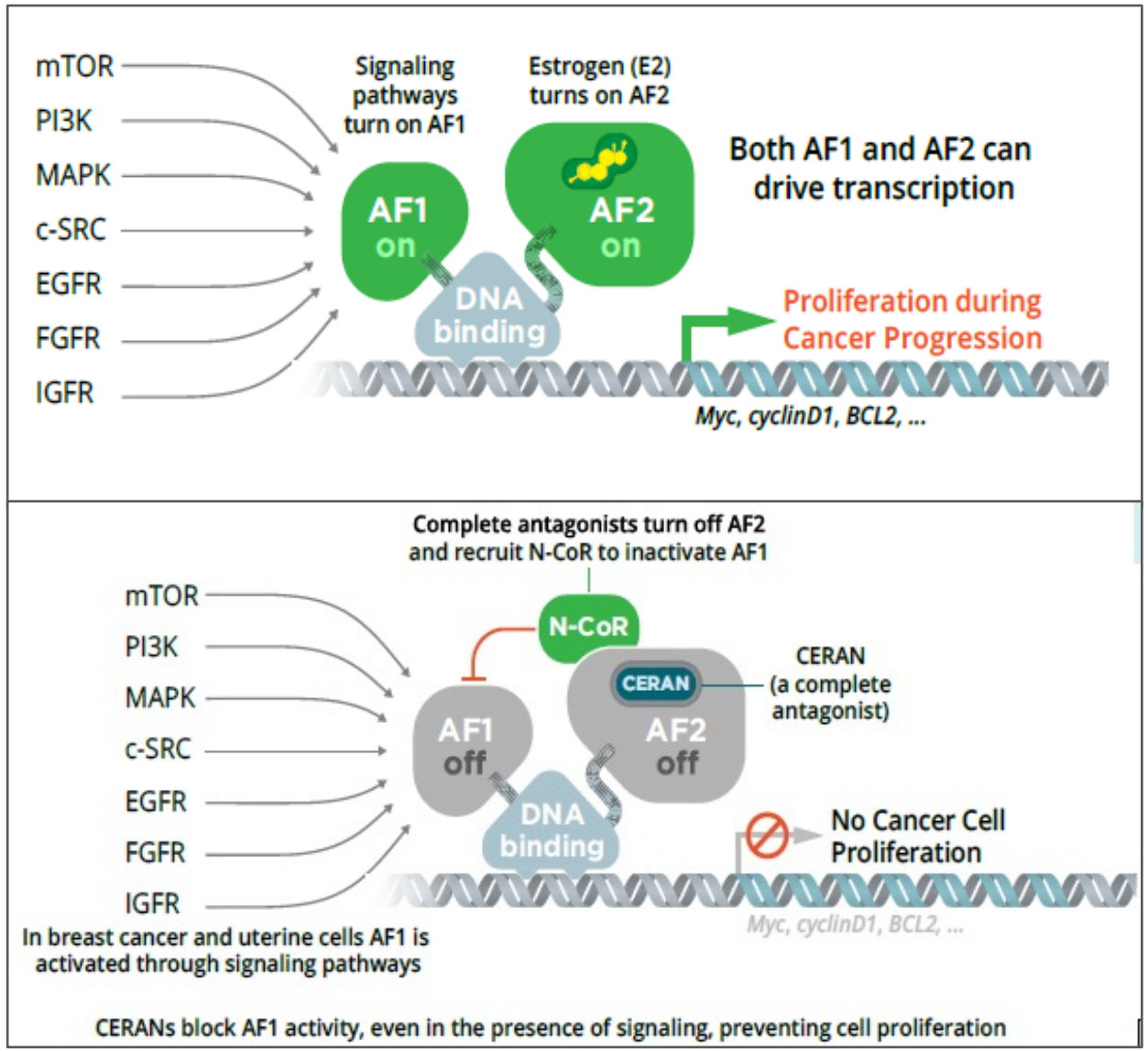
Efficacy:

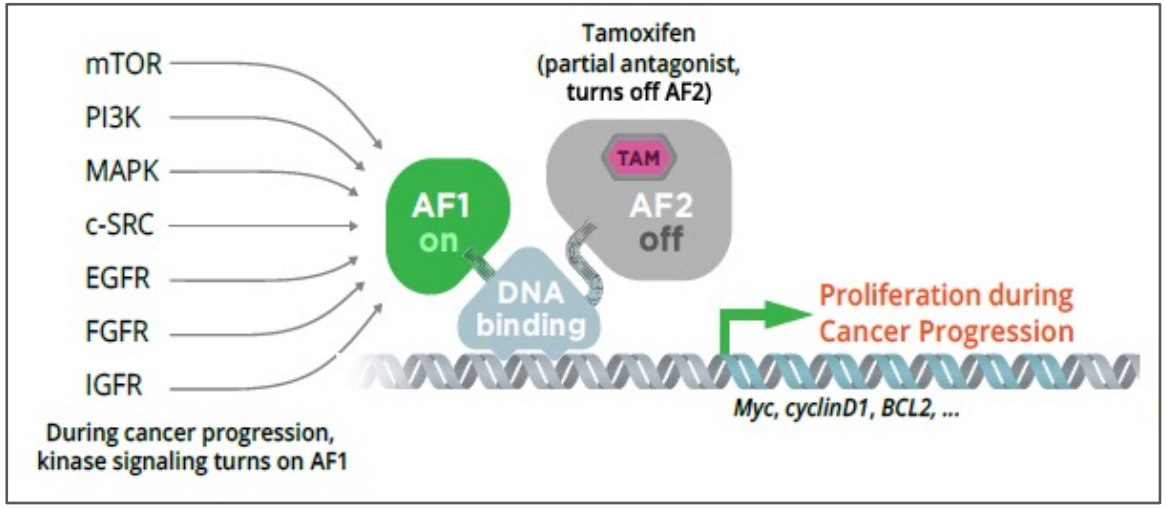
- ✓ ORR: 17%
- ✓ CBR: 40%
- ✓ mDoR: 7.5 months
- ✓ mPFS: 3.8 months
- ✓ Pts with clonal ESR1 Y537S (n=10)
- ✓ mPFS: 7.3 mo

Safety: Asymptomatic sinus bradycardia and QT prolongation were observed, reversible with tx interruption

Hamilton et al. SABCS 2021

CERAN: Complete ER antagonist- MOA





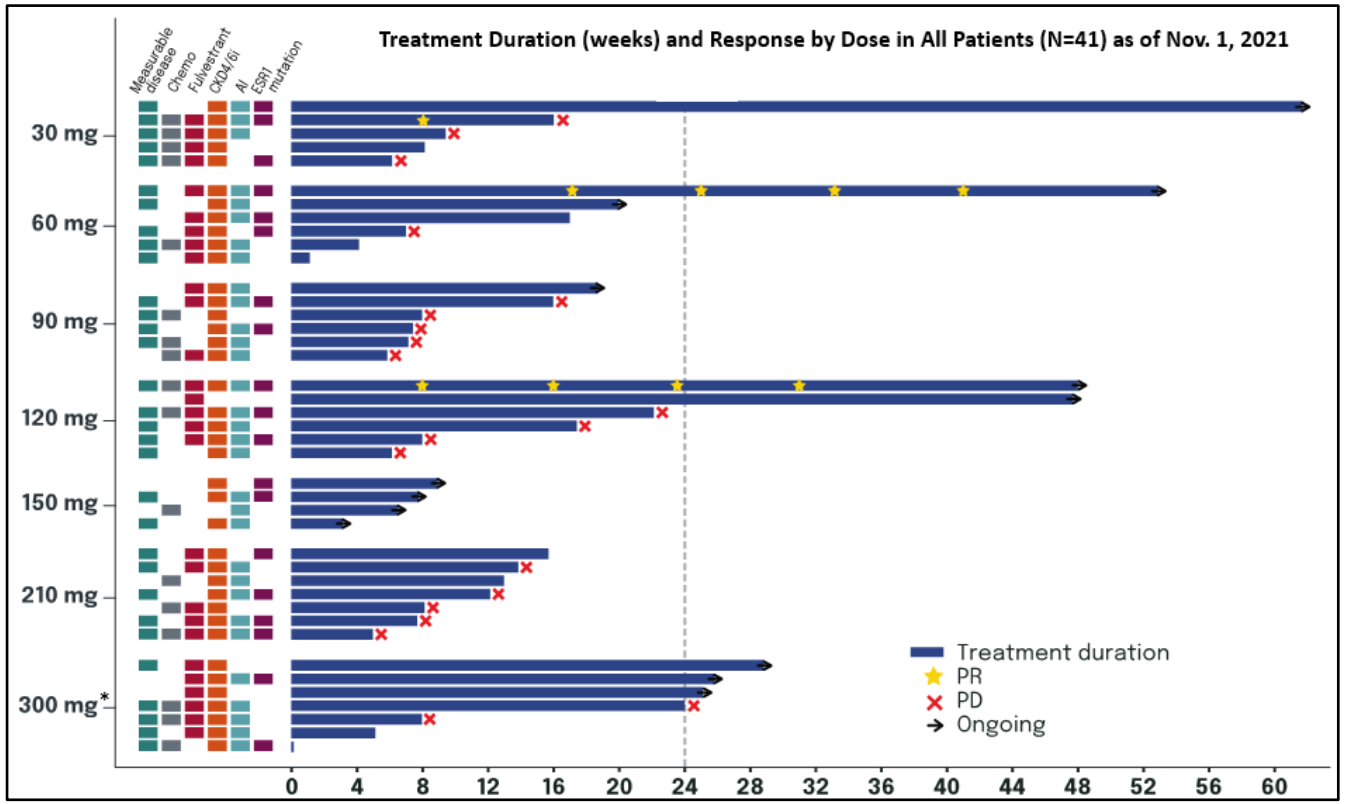
CERAN shuts down both activation functions (AF1 and AF2) of the ER

Hodges-Gallaher L et al ENA 2020

OP-1250: Durable clinical benefit in heavily pretx HR+/HER2- MBC

41 pts w/ ER/PR+ MBC tx at doses from 30mg to 300mg

- **≥3 prior lines of therapy: 37%**
- **Prior CDK 4/6i: 95%**
- **Prior fulvestrant: 68%**
- **Prior chemo: 42%**



Efficacy in RP2D range (60-120mg)

- ✓ ORR: 17%
  - ✓ **3 PRs in pts with *ESR1* mutations**
- ✓ $CBR_{24\ weeks}$: 46%

Safety:

- ✓ No DLTs observed, MTD not reached
- ✓ Most TEAEs were G1 or G2
- ✓ No clinically significant bradycardia, ocular toxicity or diarrhea

Patel MR SABCS 2021 Abstract P1-17-12

And more……

- SARM: selective androgen receptor modulator
  - Enobosarm: ORR 48%, CBR 80%, and median PFS 5.5 months in AR+++ (n=24); Phase III ARTEST trial in 3rd line metastatic setting
  - Fast track designation by FDA
- SERM: Lasofoxifene
  - Elaine 2: n=29 with abemaciclib: CBR 69% at 24 wks (ORR 50%), PFS 13 months
    - DVT 6.9% (n=2), one with risks (knee surgery etc)
  - Elaine 1: Phase II in ESR1 mut v fulvestrant

Palmieri ASCO 2021; Barroso-Sousa et al, SABCS 2021; Jhaveri et al, SABCS 2021; Damodaran et al, ASCO 2022

Potential Roadmap for ER+/HER2- MBC?

- 1st line: CDK4/6i + ET (for majority)
- 2nd line: ESR1m with duration of response to first line therapy >6 months consider elacestrant (endocrine-sensitive)
- 2nd line: consider combination strategies for patients with short response to first line therapy, or PIK3CA mutated (fulvestrant + alpelisib OR fulv/exe/tam + everolimus)
- If ESR1m + PIK3CAm ?? – Elevate trial (elacestrant combos)

Summary and Future directions

- Novel endocrine agents are in development and ultimate selection of these agents will be dependent on their optimal therapeutic index and efficacy

- Can we optimally sequence novel endocrine agents to improve outcomes?

- Understand mechanisms of resistance to these agents