EMORY
WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

Evolving Landscape in HR+/HER2- Metastatic Breast Cancer

Kevin Kalinsky, MD, MS
Professor of Medicine
Director, Glenn Family Breast Center
Director, Breast Medical Oncology
Louisa and Rand Glenn Family Chair
in Breast Cancer Research

Disclosures

- Spouse, Stock: EQRX; Grail, Array BioPharma and Pfizer (Prior Employee)
- Advisory/Consulting: Genentech/Roche, Immunomedics, Seattle Genetics, Oncosec, 4D pharma, Daicchi Saknyo, Puma Biotechnology, Mersna, Menarini Silicon Biosystems, Myovant Sciences, Takeda

What do we do after progression on CDK 4/6i?

- **Performance of endocrine monotherapy therapy post cdk 4/6 is poor; role for novel endocrine agents?**
- **Is there a role for continuation of cdk 4/6 inhibition beyond progression?**
- **Tackle endocrine resistance**

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 (Registrational)**	Positive (Non-Registrational)	Ongoing	Negative	Negative

1. Bidard FC, et al. *J Clin Oncol.* 2022;40(28):3246-3256. 2. SERENA2. 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. AMEERA3. ClinicalTrials.gov identifier: NCT04059484. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04059484; 5. Tolaney SM, et al. *Ann Oncol.* 2022; 33(7):S88-S121 (Abstr 212MO); 6. Evaluate Vantage. https://www.evaluate.com/vantage/articles/news/trial-results/roche-has-rare-breast-cancer-setback. Accessed July 20, 2022; 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(7):S88-S121 (abstr 211MO).

EMERALD Phase 3 Study Design

Inclusion Criteria

- Men and postmenopausal women with advanced/metastatic breast cancer
- ER-positive,[a] HER2-negative
- Progressed or relapsed on or after 1 or 2 lines of endocrine therapy 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[f]
- Prior treatment with fulvestrant
- Presence of visceral metastases

R

1:1[b]

Elacestrant 400 mg daily[c]

Investigator's choice (SOC):
Fulvestrant
Anastrozole
Letrozole
Exemestane

PD or withdrawal criterion[d]

Follow Up

Two Primary Endpoints:[e]

- PFS in all pts
- PFS in *ESR1*-mut

[a]Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry; [b]Recruitment from February 2019 to October 2020; [c]Protocol-defined dose reductions permitted; [d]Restaging CT scans every 8 weeks; [e]Blinded Independent Central Review; [f]*ESR1*-mutation status was determined by ctDNA analysis using the Guardant360 assay (Guardant Health, Redwood City, CA).

PFS, progression-free survival; Pts, patients; R, randomized; SOC, standard of care.

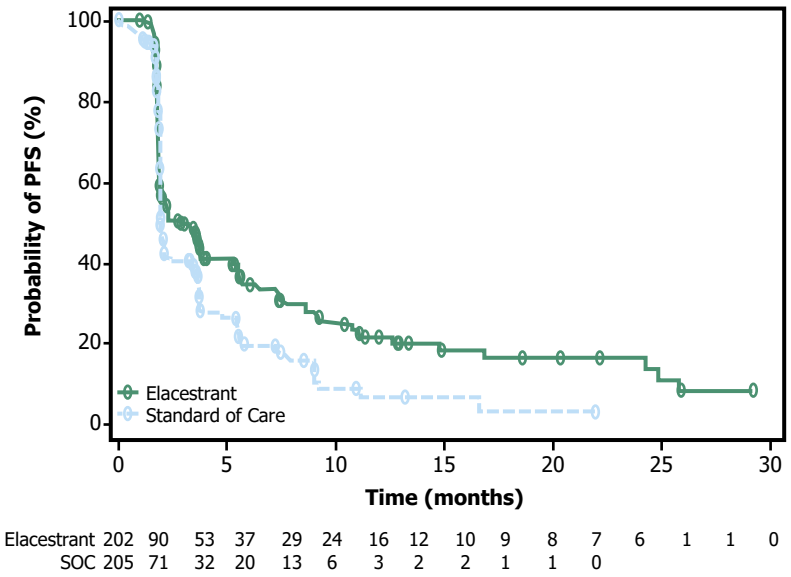
Baseline Characteristics

Parameter	Elacestrant		SOC	
	All (N=239)	*ESR1*-mut (N=115)	All (N=239)	*ESR1*-mut (N=113)
Median age, years (range)	63.0 (24-89)	64.0 (28-89)	63.0 (32-83)	63.0 (32-83)
Gender, n (%) Female Male	233 (97.5) 6 (2.5)	115 (100) 0	238 (99.6) 1 (0.4)	113 (100) 0
ECOG PS, n (%) 0 1 >1	143 (59.8) 96 (40.2) 0	67 (58.3) 48 (41.7) 0	135 (56.5) 103 (43.1) 1 (0.4)	62 (54.9) 51 (45.1) 0
Visceral metastasis*, n (%)	163 (68.2)	81 (70.4)	170 (71.1)	84 (74.3)
Prior CDK4/6i, n (%)	239 (100)	115 (100)	239 (100)	113 (100)
Number of prior lines of endocrine therapy,** n (%) 1 2	129 (54.0) 110 (46.0)	73 (63.5) 42 (36.5)	142 (59.4) 97 (40.6)	69 (61.1) 44 (38.9)
Type of prior endocrine therapy, n (%)**				
Fulvestrant	**70 (29.3)**	**27 (23.5)**	**75 (31.4)**	**28 (24.8)**
AI Tamoxifen	193 (80.8) 19 (7.9)	101 (87.8) 9 (7.8)	194 (81.2) 15 (6.3)	96 (85.0) 9 (8.0)
Number of prior lines of chemotherapy,** n (%) 0 1	191 (79.9) 48 (20.1)	89 (77.4) 26 (22.6)	180 (75.3) 59 (24.7)	81 (71.7) 32 (28.3)

*Includes lung, liver, brain, pleural, and peritoneal involvement
**In the advanced/metastatic setting

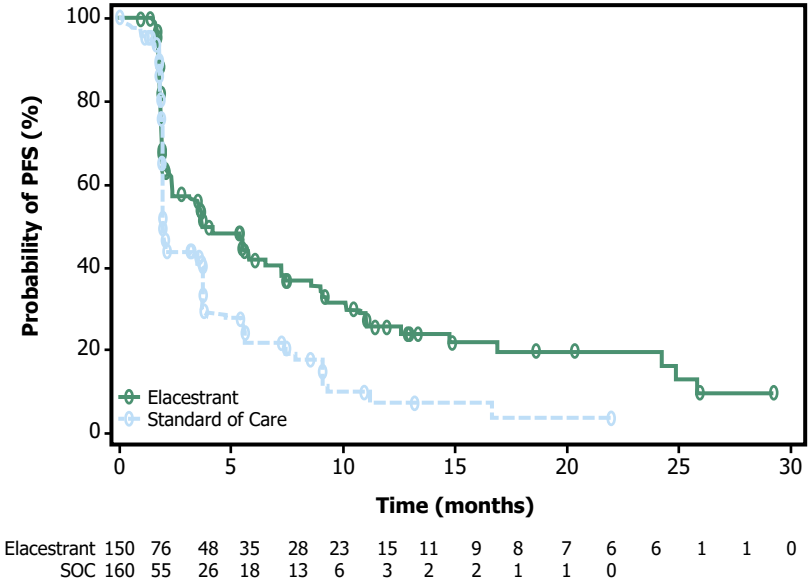
All Patients: PFS by Duration of CDK4/6i

At least 6 mo CDK4/6i



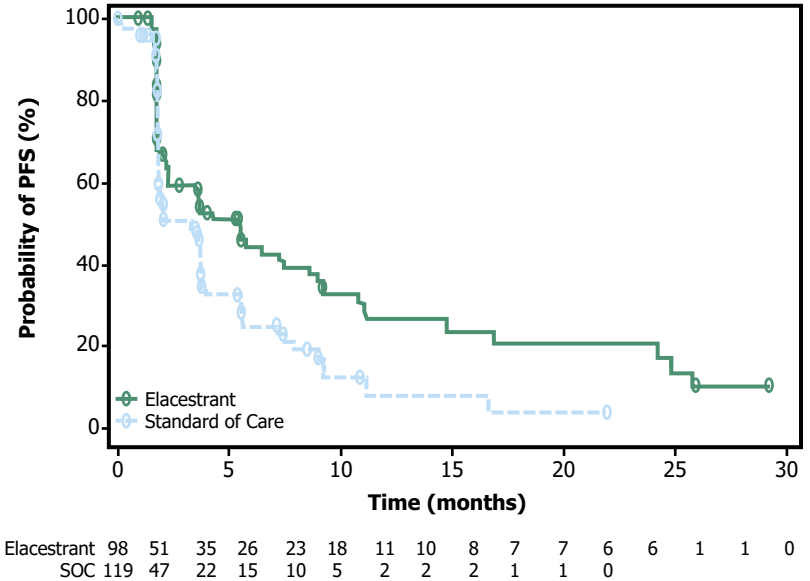
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**2.79** (1.94 - 3.78)	**1.91** (1.87 - 2.14)
PFS rate at 12 months, % (95% CI)	21.00 (13.57 - 28.43)	6.42 (0.75 - 12.09)
Hazard ratio (95% CI)	**0.688** (0.535 - 0.884)	

At least 12 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**3.78** (2.33 - 6.51)	**1.91** (1.87 - 3.58)
PFS rate at 12 months, % (95% CI)	25.64 (16.49 - 34.80)	7.38 (0.82 - 13.94)
Hazard ratio (95% CI)	**0.613** (0.453 - 0.828)	

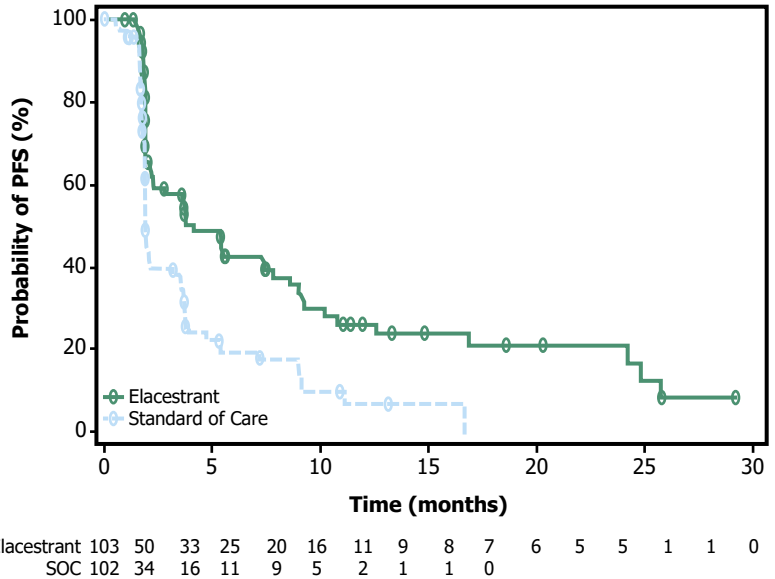
At least 18 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**5.45** (2.33 - 8.61)	**3.29** (1.87 - 3.71)
PFS rate at 12 months, % (95% CI)	26.70 (15.61 - 37.80)	8.23 (0.00 - 17.07)
Hazard ratio (95% CI)	**0.703** (0.482 - 1.019)	

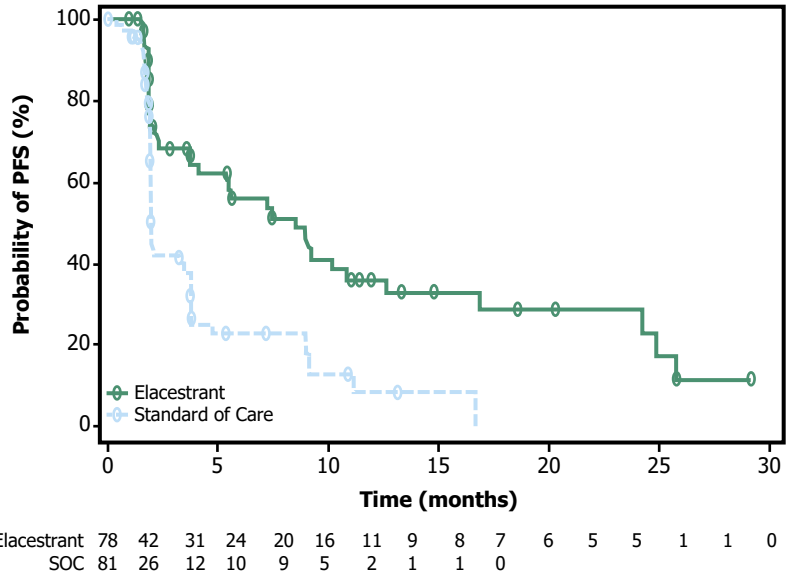
Patients with *ESR1*-mut Tumors: PFS by Duration of CDK4/6i

At least 6 mo CDK4/6i



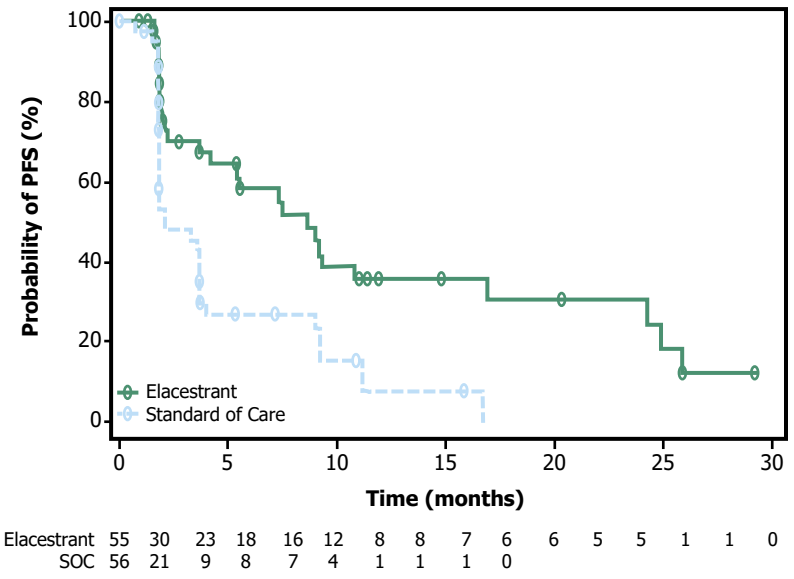
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

At least 12 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)
PFS rate at 12 months, % (95% CI)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)
Hazard ratio (95% CI)	**0.410** (0.262 - 0.634)	

At least 18 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 12 months, % (95% CI)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
Hazard ratio (95% CI)	**0.466** (0.270 - 0.791)	

RIGHT Choice study design

- Pre-/perimenopausal women
- HR+/ HER2– ABC (>10% ER+)
- No prior systemic therapy for ABC
- Measurable disease per RECIST 1.1
- Aggressive disease[a]
  - Symptomatic visceral metastases
  - Rapid disease progression or impending visceral compromise
  - Markedly symptomatic non-visceral disease
- ECOG PS ≤ 2[b]
- Total bilirubin ≤ 1.5 ULN
- N = 222[c]

Stratified by (1) the presence or absence of liver metastases and by (2) DFI[d] < or ≥2 years

R 1:1

Ribociclib
(600 mg, 3 weeks on/1 week off)
+
Letrozole or anastrozole + goserelin

Investigators' choice of combination CT[e]

Docetaxel + capecitabine
Paclitaxel + gemcitabine
Capecitabine + vinorelbine

Tumor imaging evaluation
Q6W for 1st 12 weeks, Q8W for next 32 weeks, then Q12W[f]

Primary endpoint
- PFS (locally assessed per RECIST 1.1)

Secondary endpoints
- TTF
- 3-month TFR
- ORR
- CBR
- TTR
- OS
- Safety
- QOL

Exploratory endpoints
- Biomarker analyses
- Healthcare resource utilization

ABC, advanced breast cancer; CBR, clinical benefit rate; CT, chemotherapy; DFI, disease-free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ER+, estrogen receptor positive; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q6W, every 6 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; QOL, quality of life; RECIST, Response Evaluation Criteria In Solid Tumors; TFR, treatment failure rate; TTF, time to treatment failure; TTR, time to response; ULN, upper limit of normal.
[a] Where combination CT is clinically indicated by physician's judgment; [b] For patients with ECOG 2, the poor performance status should be due to breast cancer; [c] Patients were enrolled from Feb 2019 to Nov 2021; [d] Disease-free interval is defined as the duration from date of complete tumor resection for primary breast cancer lesion to the date of documented disease recurrence; [e] If one of the combination CT drugs had to be stopped because of toxicity, the patient was allowed to continue on the other, better-tolerated CT drug (monotherapy); [f] Until disease progression, death, withdrawal of consent, loss to follow-up, or patient/guardian decision, and at end of treatment.

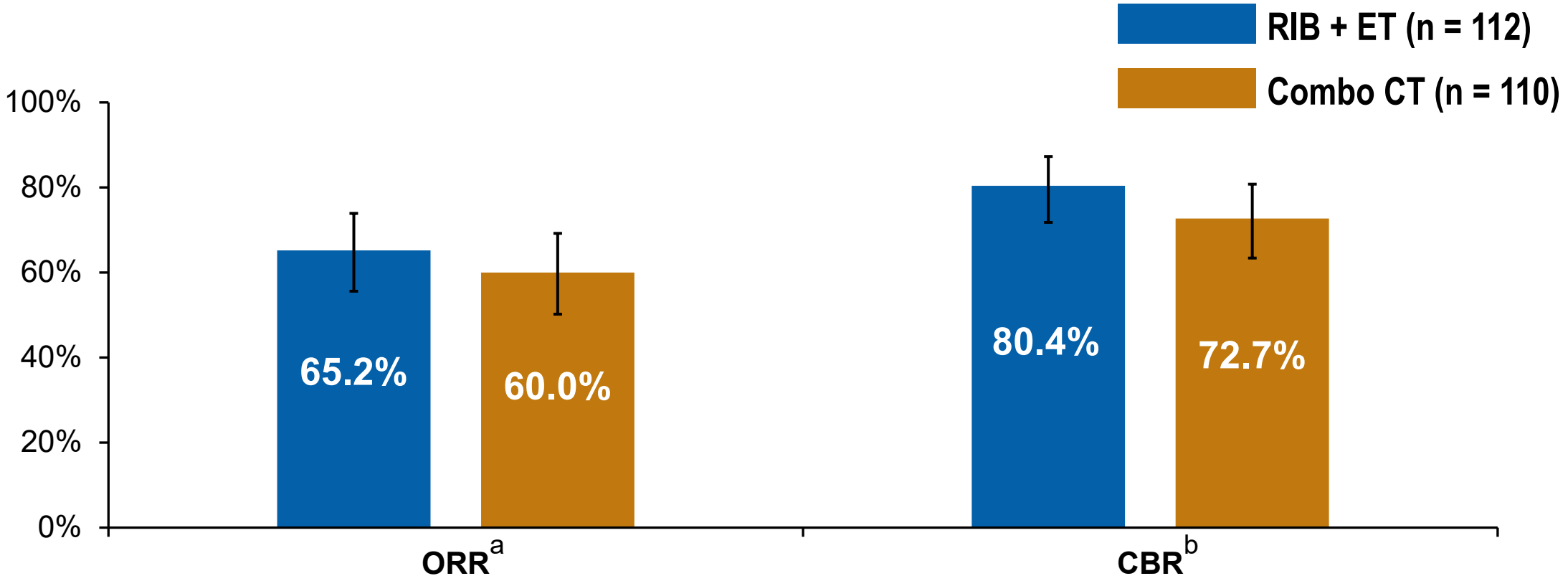
Baseline characteristics were well balanced

Parameter, n (%)	RIB + ET n = 112	Combo CT n = 110
Median age, years	44.0	43.0
≥40 years	80 (71.4)	72 (65.5)
Race[a]		
Asian	60 (53.6)	58 (52.7)
White	51 (45.5)	52 (47.3)
Histological grade		
Grade 1	10 (8.9)	16 (14.5)
Grade 2	66 (58.9)	61 (55.5)
Grade 3	35 (31.3)	29 (26.4)
≥50% ER+	95 (84.8)	95 (86.4)
PR+	99 (88.4)	102 (92.7)

Parameter, n (%)	RIB + ET n = 112	Combo CT n = 110
Disease status		
De novo	71 (63.4)	73 (66.4)
Visceral metastatic sites[b]		
Liver	56 (50.0)	57 (51.8)
Lung	63 (56.3)	58 (52.7)
Liver or lung	89 (79.5)	85 (77.3)
Aggressive disease characteristic		
Rapid progression	23 (20.5)	18 (16.4)
Symptomatic non-visceral disease	15 (13.4)	16 (14.5)
Symptomatic visceral metastases	74 (66.1)	76 (69.1)
Visceral crisis[c]	61 (54.5)	55 (50.0)

Combo CT, combination chemotherapy; ER+, estrogen receptor positive; ET, endocrine therapy; RIB, ribociclib.
[a] One patient (0.9%) in the RIB arm was African American; [b] The same patient may have multiple visceral metastatic sites. [c] Based on PI's judgment, which followed ABC3 and NCCN guidelines, which were available at the time of study design.

ORR and CBR were similar between RIB + ET and combination CT

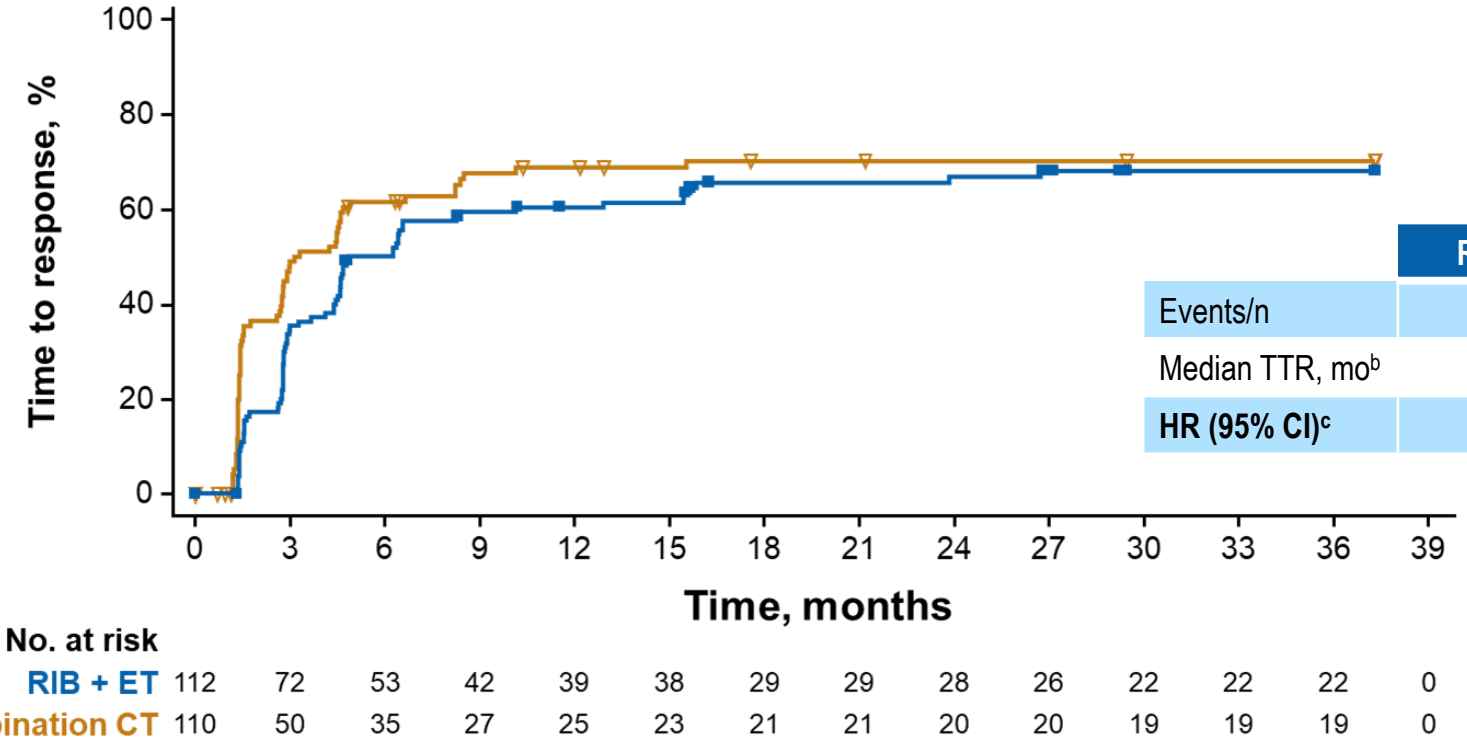


- A sensitivity analysis[c] confirmed the ORR and CBR findings in the safety set

CBR, clinical benefit rate; Combo CT, combination chemotherapy; CR, complete response; ET, endocrine therapy; ORR, overall response rate; PD, progressive disease; PR, partial response, RIB, ribociclib; SD, stable disease.

[a] Proportion of patients with CR or PR without confirmation (confirmation imaging was not mandatory according to study protocol); [b] Proportion of patients with CR or PR without confirmation or SD or non-CR/non-PD ≥24 weeks; [c] This analysis included all patients who received ≥1 dose of any component of the study treatment (safety set).

Time to onset of response (TTR) for RIB + ET was similar to combination CT



	RIB + ET	Combo CT
Events/n	73/112	66/110[a]
Median TTR, mo[b]	4.9	3.2
HR (95% CI)[c]	**0.78 (0.56-1.09)**	

- A sensitivity analysis[d] confirmed the TTR findings in the safety set

Combo CT, combination chemotherapy; CR, complete response, ET, endocrine therapy; HR, hazard ratio; IRT, interactive response technology; PR, partial response; RIB, ribociclib.
[a] Ten patients in CT arm did not receive any treatment; [b] TTR is defined as the time from the date of randomization to the first documented response of either CR or PR without confirmation (confirmation imaging was not required according to study protocol); [c] HR is obtained from Cox Proportional-Hazards model stratified by liver metastasis and disease-free interval per IRT; [d] The sensitivity analysis excluded the 10 patients in the CT arm who did not receive any treatment and were removed from the denominator for the CT arm.

Changing CDK4/6*i* after CDK 4/6*i* – Pace Trial (Ph II)

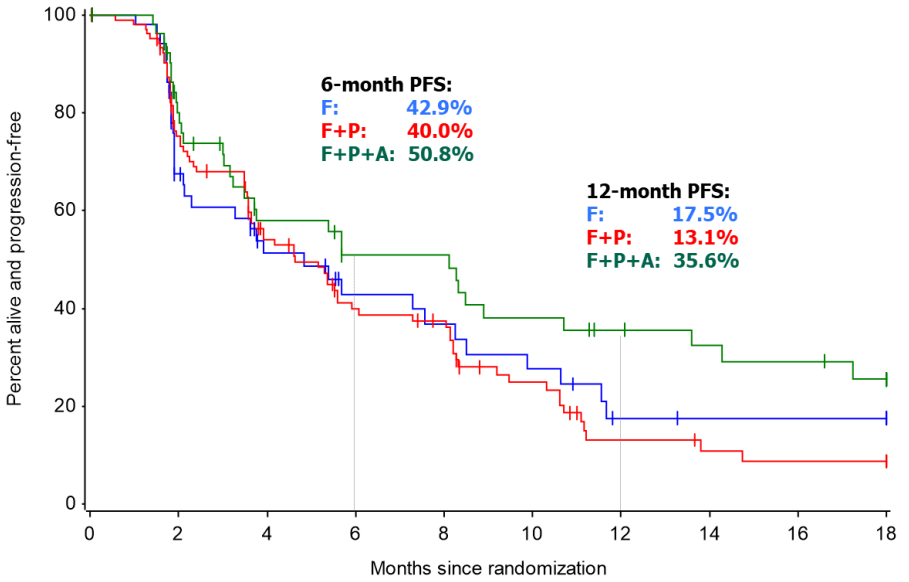
Aim: (1) Role of maintaining CDK4/6i beyond progression, with change of ET to fulvestrant, (2) adding ICPi

Eligibility Criteria
- HR+/HER2- MBC
- Progression on CDK4/6i and ET, with ≥6mo SD on prior regimen
- ≤2 prior lines ET for MBC
- No prior fulvestrant
- 0-1 prior chemo for MBC

N=220

RANDOMIZE

- **Fulvestrant**
- **Fulvestrant Palbociclib**
- **Fulvestrant Palbociclib Avelumab**



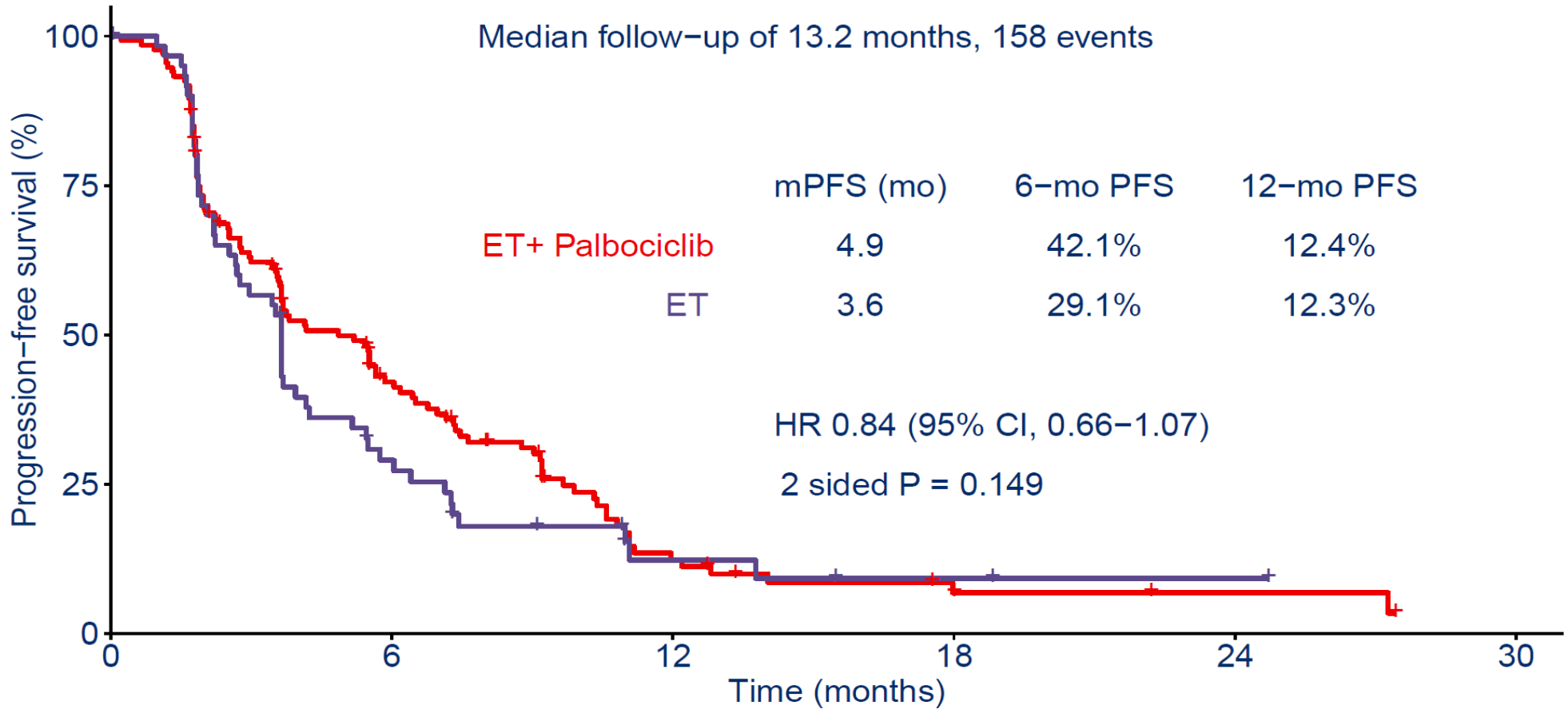
Patient/tumour characteristics	Prior CDK4/6i therapy	Guardant 360 ctDNA
80% postmenopausal	Palbo 90%	54% *ESR1* alteration
60% visceral disease	Prior CDK4/6i for >12m in 75%	35% *PIK3CA* alteration
15% 1 prior chemo for MBC	88% went straight from prior CDK4/6i to PACE	11% *RB1* alteration

	Pts	PFS Events	Median PFS, mo (90% CI)	HR vs F (90% CI)	P-value
F	55	34	**4.8** (2.1, 8.2)	--	--
F+P	111	79	**4.6** (3.6, 5.9)	1.11 (0.74-1.66)	P=0.62
F+P+A	54	35	**8.1** (3.2, 10.7)	0.75 (0.47-1.20)	P=0.23

Combining palbociclib with fulvestrant beyond progression on prior CDK4/6i did not significantly improve PFS compared with using fulvestrant alone.

Mayer E et al. SABCS 2022, #GS3-06

Primary Objective: Investigator-assessed PFS (ITT Population)



Patients at risk, n (%)

ET+Palbociclib	136 (100)	47 (35)	11 (8)	4 (3)	2 (1)	0 (0)
ET	62 (100)	16 (26)	4 (6)	2 (3)	1 (2)	0 (0)

CI: Confidence interval; HR: Hazard ratio; ITT: Intention to treat; mo: Months; mPFS: Median progression-free survival; PFS: Progression-free survival.

Changing CDK4/6*i* And ET after CDK 4/6*i* - The MAINTAIN-trial (Ph II)

Key Entry Criteria

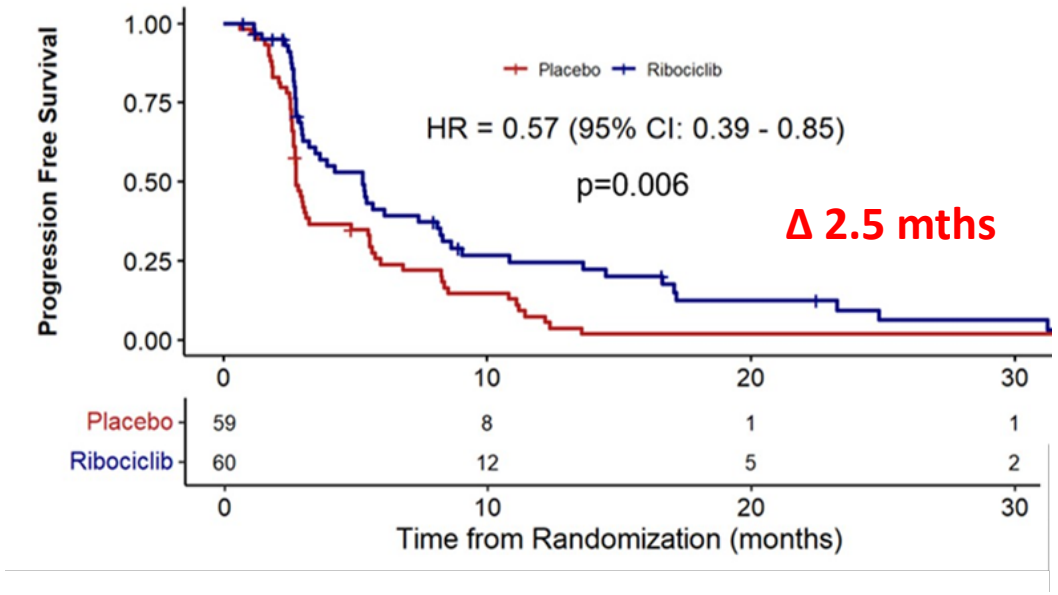
- **Progression on ET + any CDK 4/6 inhibitor**
- ER and/or PR ≥ 1%, HER2- MBC
- ≤ 1 line of chemo for MBC
- Measurable or non-measurable
- Postmeno or premeno and GnRHa

1:1

N=120

Arm 1
Ribociclib + Switch Endo Tx

Arm 2
Placebo + Switch Endo Tx



87% of the pts received prior palbociclib
83% of the pts switched to Fulvestrant
66% were treated prior with CDK 4/6i >12 mths

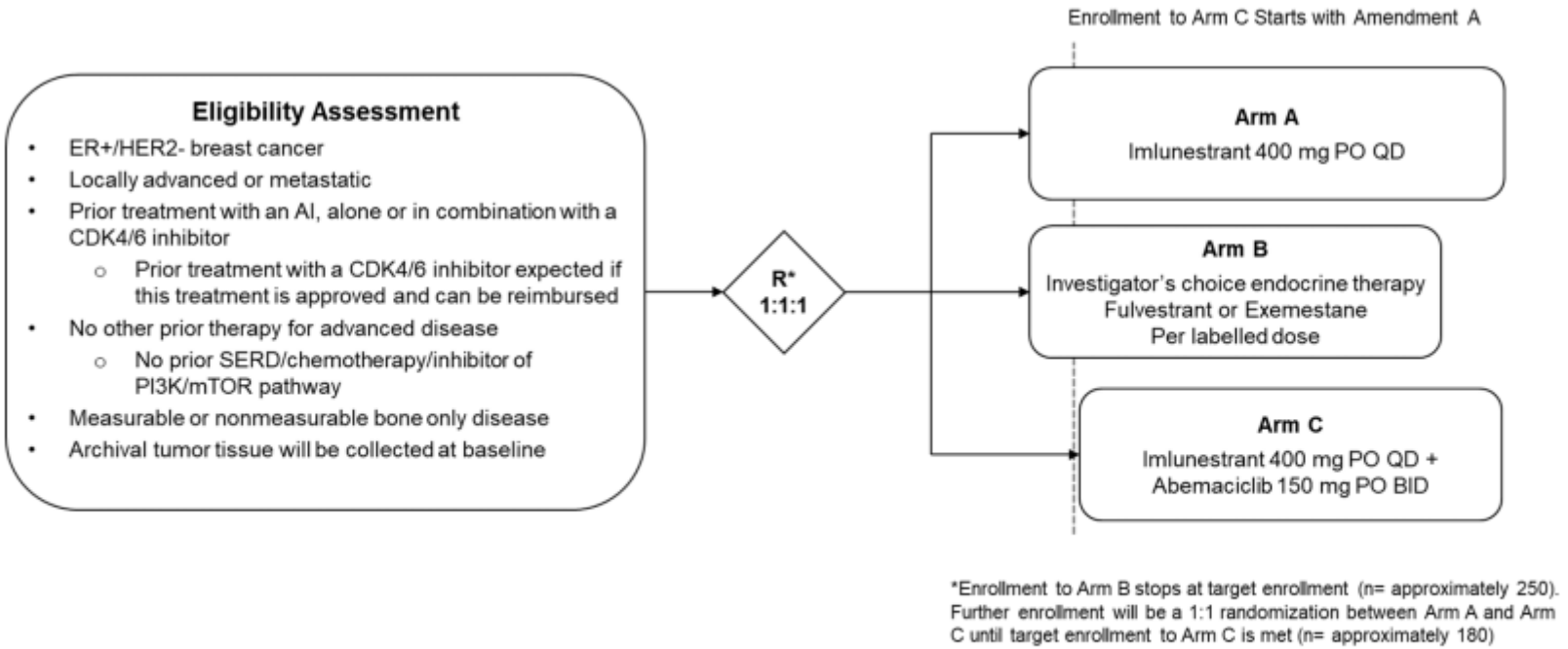
	ET+ Placebo	ET+ Ribo
Median PFS months (95% CI)	**2.76 (2.66-3.25)**	**5.29 (3.02-8.12)**
PFS rate at 6 months	23.9%	41.2%
PFS rate at 12 months	7.4%	24.6%

Kalinsky K et al ASCO 2022,#LBA1004

Ongoing Trials

Await data from larger randomized phase 3trials postMONARCH: Fulvestrant + Abema vs Fulvestrant

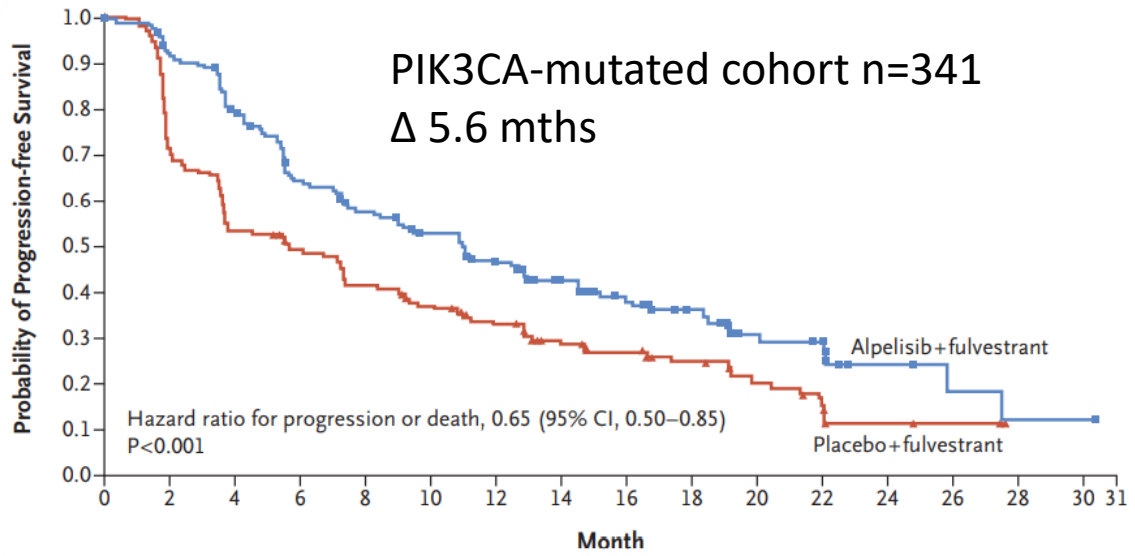
N= 860



Note: *ESR1* mutation status will be centrally determined in plasma by Guardant 360 ctDNA assay from a blood draw at baseline.

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

Phase 3 Capitello-291: Prior treatments

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence or progression while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

Stratification factors:
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region*

Capivasertib	400 mg twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks
Placebo	Twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks

Dual primary endpoints

PFS by investigator assessment
- Overall
- AKT pathway-altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

Key secondary endpoints

Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

Characteristic		Overall population		AKT pathway-altered population	
		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
Prior endocrine therapy for ABC; n (%)	0	40 (11.3)	54 (15.3)	14 (9.0)	20 (14.9)
	1	286 (80.6)	252 (71.4)	130 (83.9)	96 (71.6)
	2	29 (8.2)	47 (13.3)	11 (7.1)	18 (13.4)
Previous CDK4/6 inhibitor for ABC; n (%)		245 (69.0)	244 (69.1)	113 (72.9)	91 (67.9)
Previous chemotherapy; n (%)	Adjuvant/neoadjuvant	180 (50.7)	170 (48.2)	79 (51.0)	67 (50.0)
	ABC	65 (18.3)	64 (18.1)	30 (19.4)	23 (17.2)

Turner et al SABCS 2022

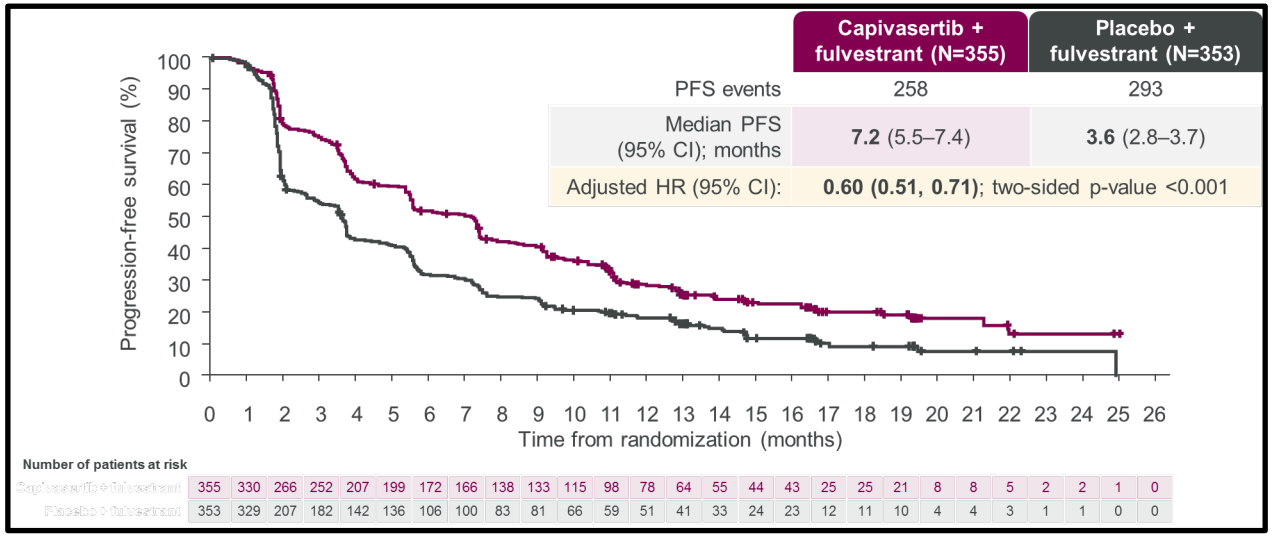
Phase 3 Capitello-291: AKT pathway alterations

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)

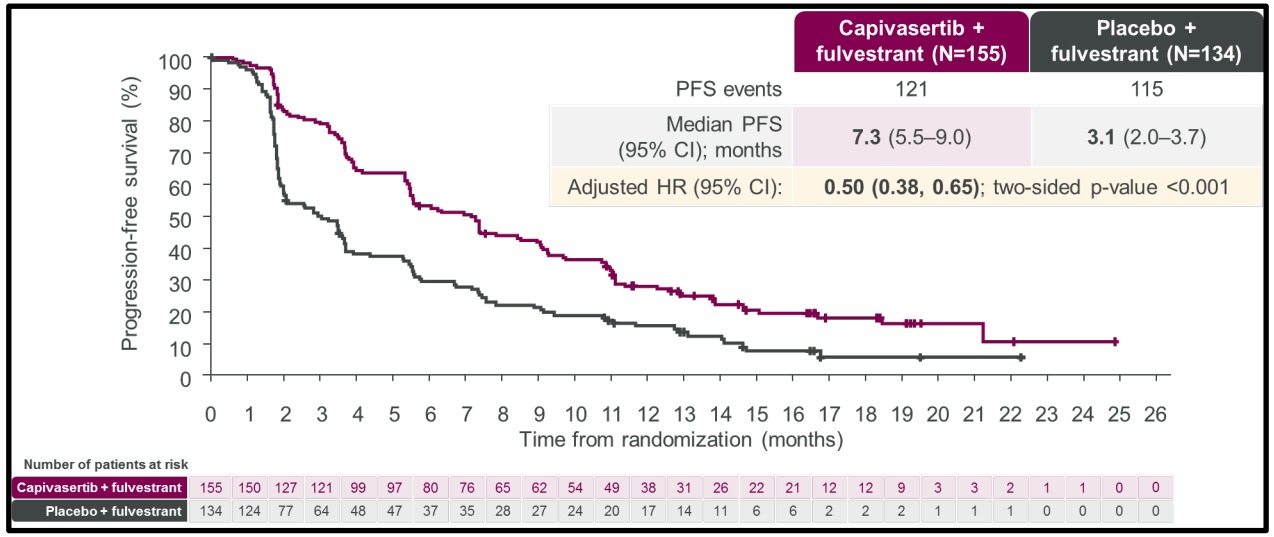
AKT pathway alteration status was determined centrally using next-generation sequencing in tumor tissue with the FoundationOne®CDx assay (and Burning Rock assay in China)

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



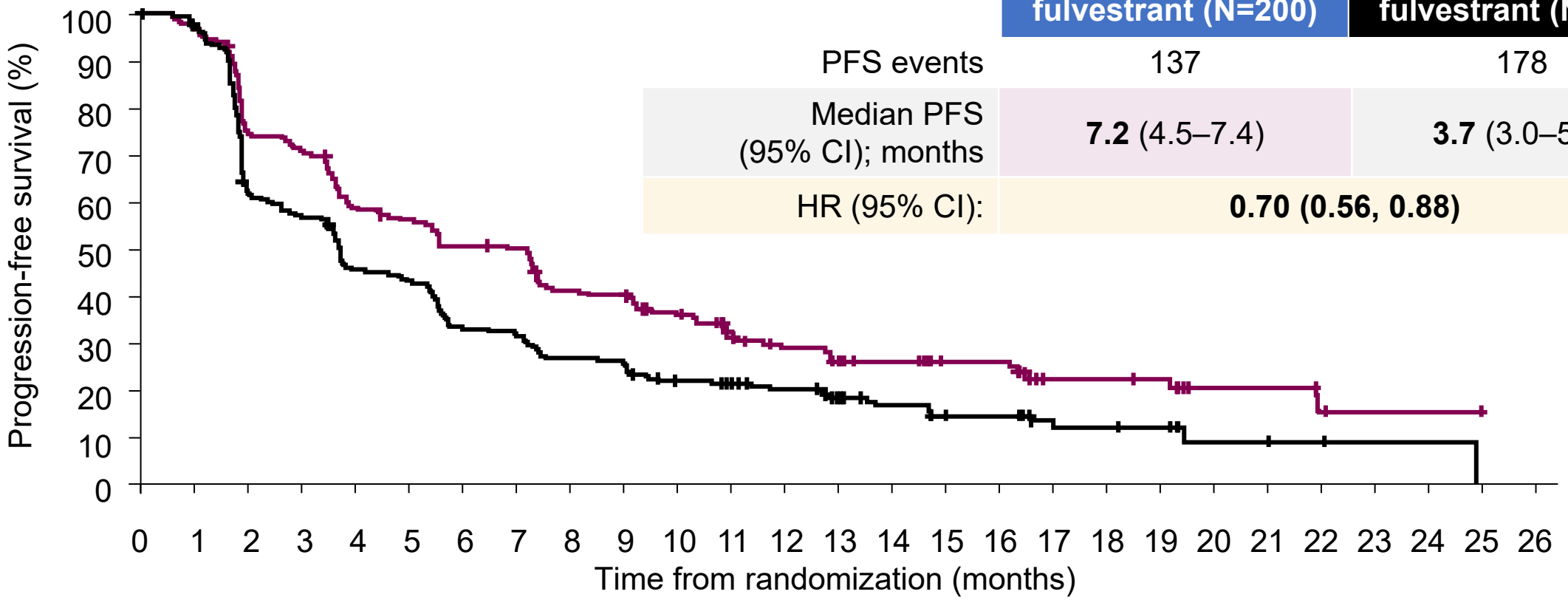
AKT pathway-altered population

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

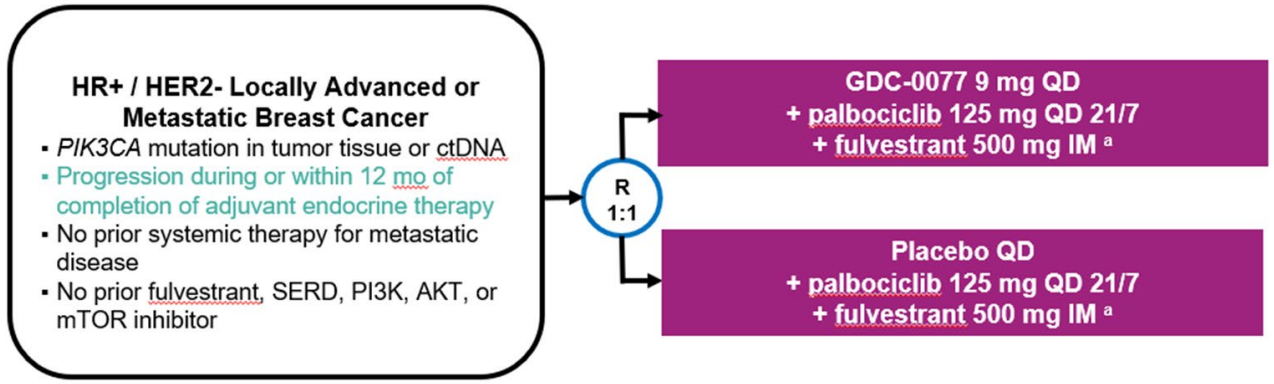
+ indicates a censored observation. †Patients with no valid NGS results. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and prior use of CDK4/6 inhibitor.

Turner et al SABCS 2022

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

Triplet Strategies with CDK4/6i + PI3Ki/Akti + Fulvestrant ongoing in 1L

WO41554: Study Design Inavolisib: αPI3Ki



N = 400

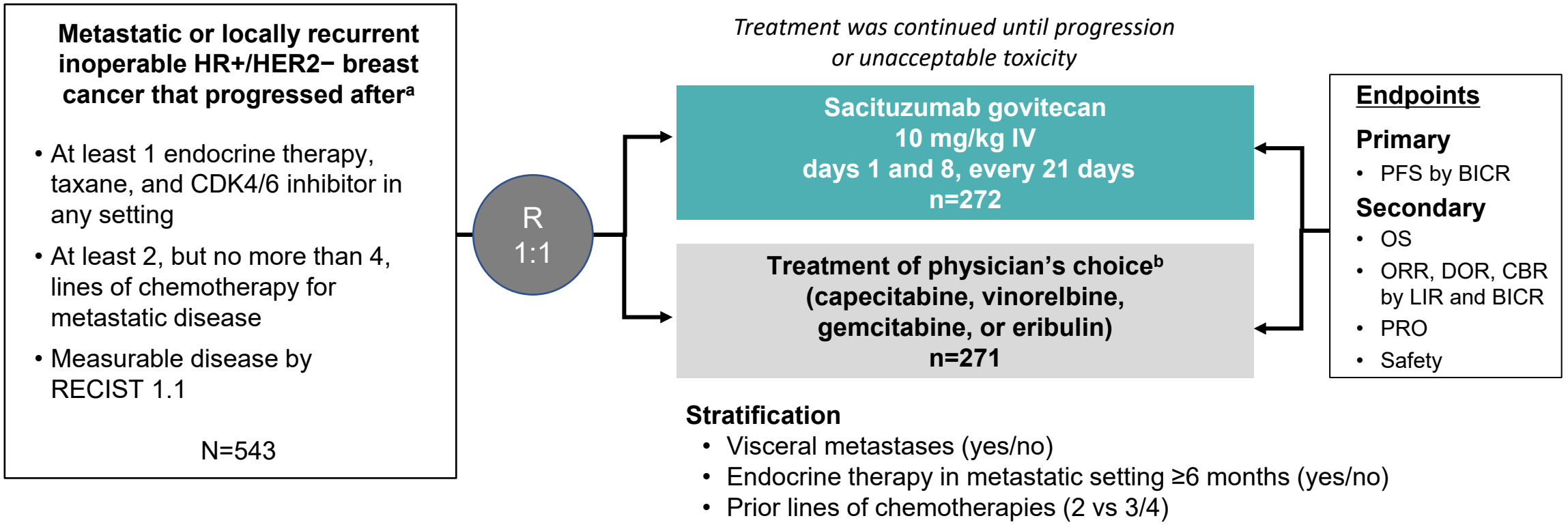
Stratification factors

1. Visceral disease [b]
2. Endocrine resistance: primary vs. secondary [c]
3. Region

Principle Objectives	Efficacy, safety
Primary Endpoint	Investigator-assessed PFS
Secondary Endpoints	• ORR, DoR • PRO • OS

ClinicalTrials.gov Identifier: NCT04191499

TROPiCS-02: A Phase 3 Study of SG in HR+/HER2− Locally Recurrent Inoperable or Metastatic Breast Cancer

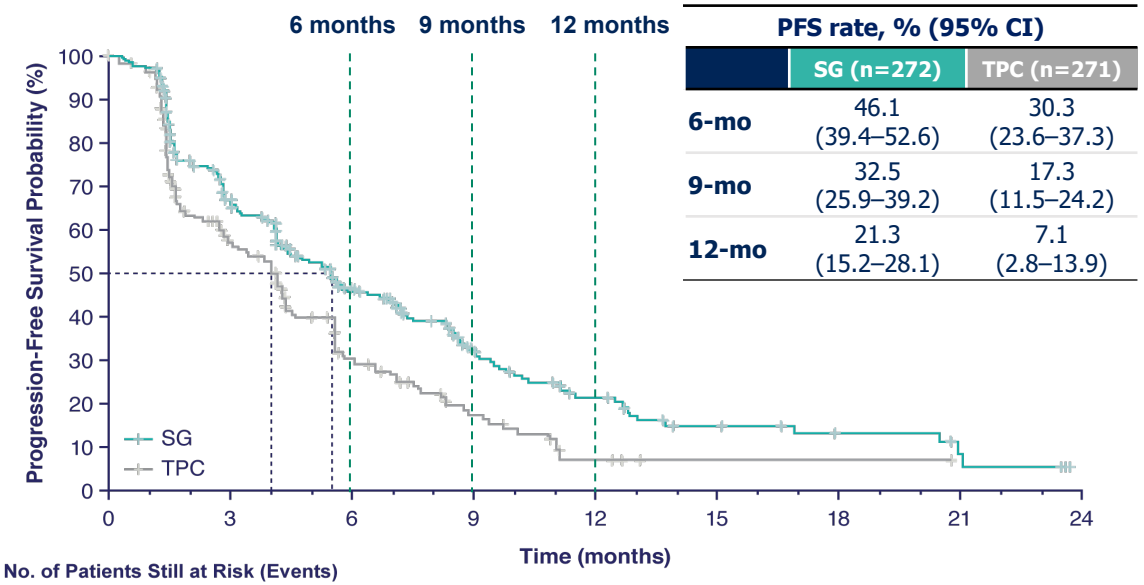


[a]Disease histology based on ASCO/CAP criteria. [b]Single-agent standard-of-care treatment of physician's choice was specified prior to randomization by the investigator.
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; DOR, duration of response; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormonal receptor-positive; IV, intravenously; LIR, local investigator review; (neo)adjuvant, neoadjuvant or adjuvant; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcomes; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.

PFS & OS in the ITT Population

PFS[1]

BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	*P*=0.0003	



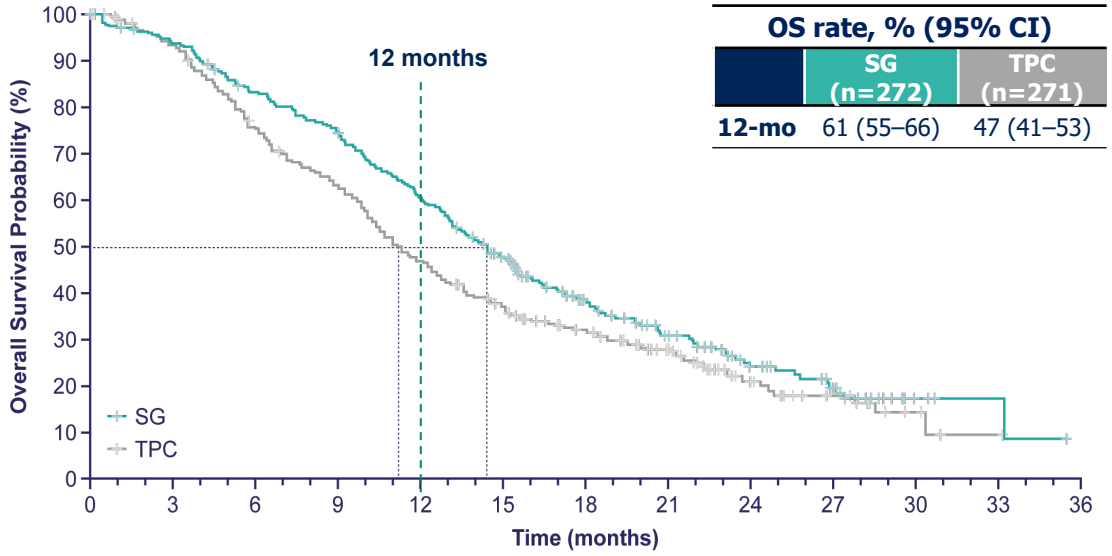
PFS rate, % (95% CI)	SG (n=272)	TPC (n=271)
6-mo	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-mo	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-mo	21.3 (15.2–28.1)	7.1 (2.8–13.9)

No. of Patients Still at Risk (Events)

SG	272 (0)	148 (83)	82 (124)	44 (146)	22 (160)	12 (166)	6 (167)	3 (169)	0 (170)
TPC	271 (0)	105 (91)	41 (136)	17 (151)	4 (159)	1 (159)	1 (159)	0 (159)	

OS[2]

	SG (n=272)	TPC (n=271)
Median OS, mo (95% CI)	14.4 (13.0–15.7)	11.2 (10.1–12.7)
Stratified HR (95% CI)	**0.79** (0.65–0.96)	
Stratified Log Rank *P* value	*P*=0.020	



OS rate, % (95% CI)	SG (n=272)	TPC (n=271)
12-mo	61 (55–66)	47 (41–53)

No. of Patients Still at Risk (Events)

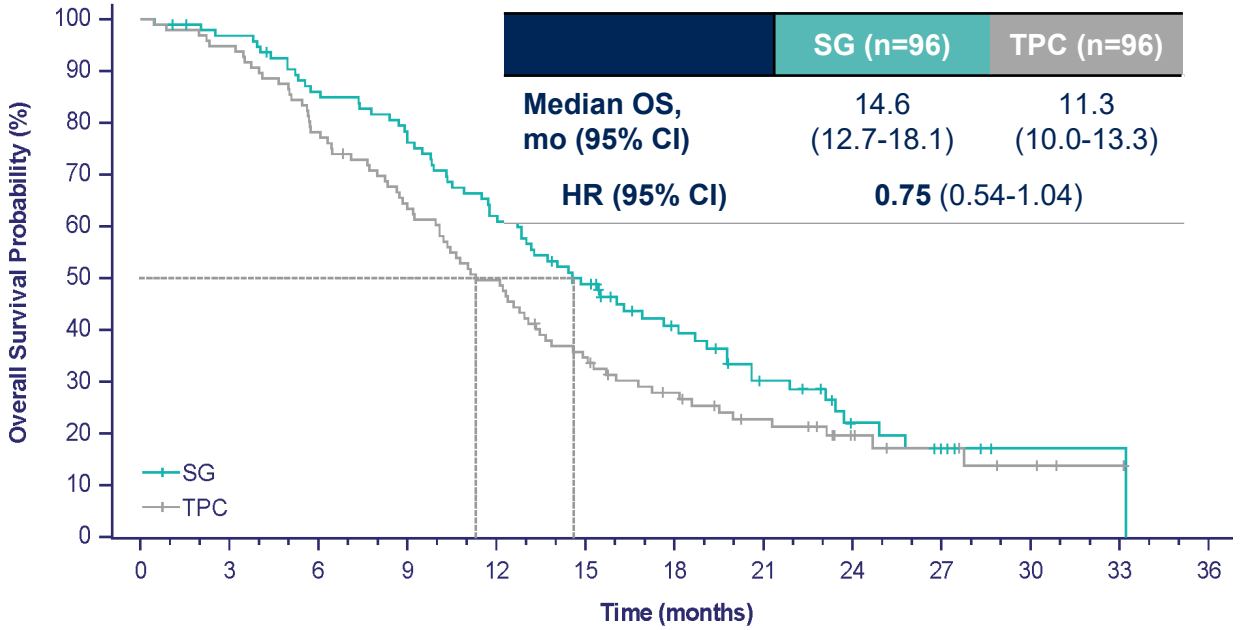
SG	272 (0)	252 (16)	221 (44)	197 (67)	160 (104)	120 (137)	80 (158)	53 (173)	31 (183)	20 (188)	4 (190)	2 (190)	0 (191)
TPC	271 (0)	246 (16)	196 (64)	164 (95)	122 (137)	92 (163)	70 (174)	49 (183)	23 (193)	13 (196)	5 (198)	1 (199)	0 (199)

SG demonstrated a statistically significant improvement in PFS and OS vs TPC

Median follow-up was 10.2 months.
BICR, blinded independent central review; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
1. Rugo HS, et al. *J Clin Oncol.* 2022;40:3365-3376. Adapted from Rugo HS, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol. 2022*. doi: 10.1200/JCO.22.01002. Reprinted with permission from American Society of Clinical Oncology. 2. Rugo H, et al. ESMO 2022. Oral LBA76.

Overall Survival: Trop-2 H-Score Cutoff of 100

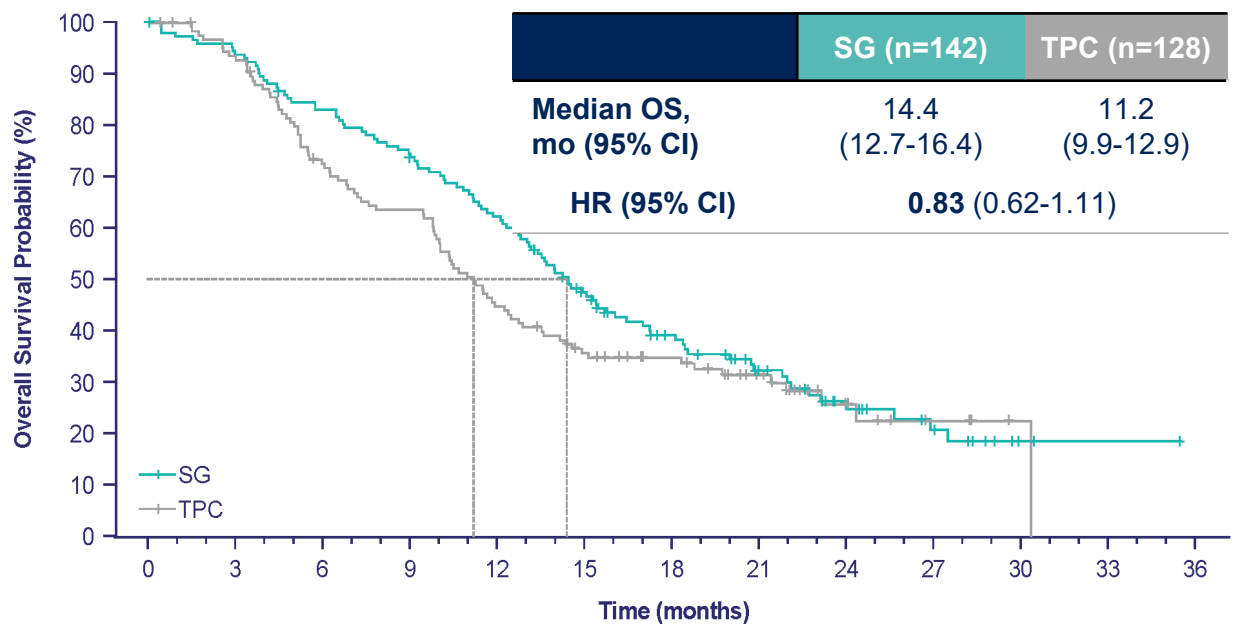
<100 Subgroup



No. of Patients Still at Risk (Events)

SG	96 (0)	90 (3)	79 (13)	72 (20)	57 (35)	43 (47)	28 (53)	18 (60)	9 (64)	5 (66)	1 (66)	1 (66)	0 (67)
TPC	96 (0)	91 (5)	75 (21)	61 (34)	47 (48)	32 (62)	23 (68)	16 (72)	9 (74)	6 (75)	3 (76)	1 (76)	0 (76)

≥100 Subgroup



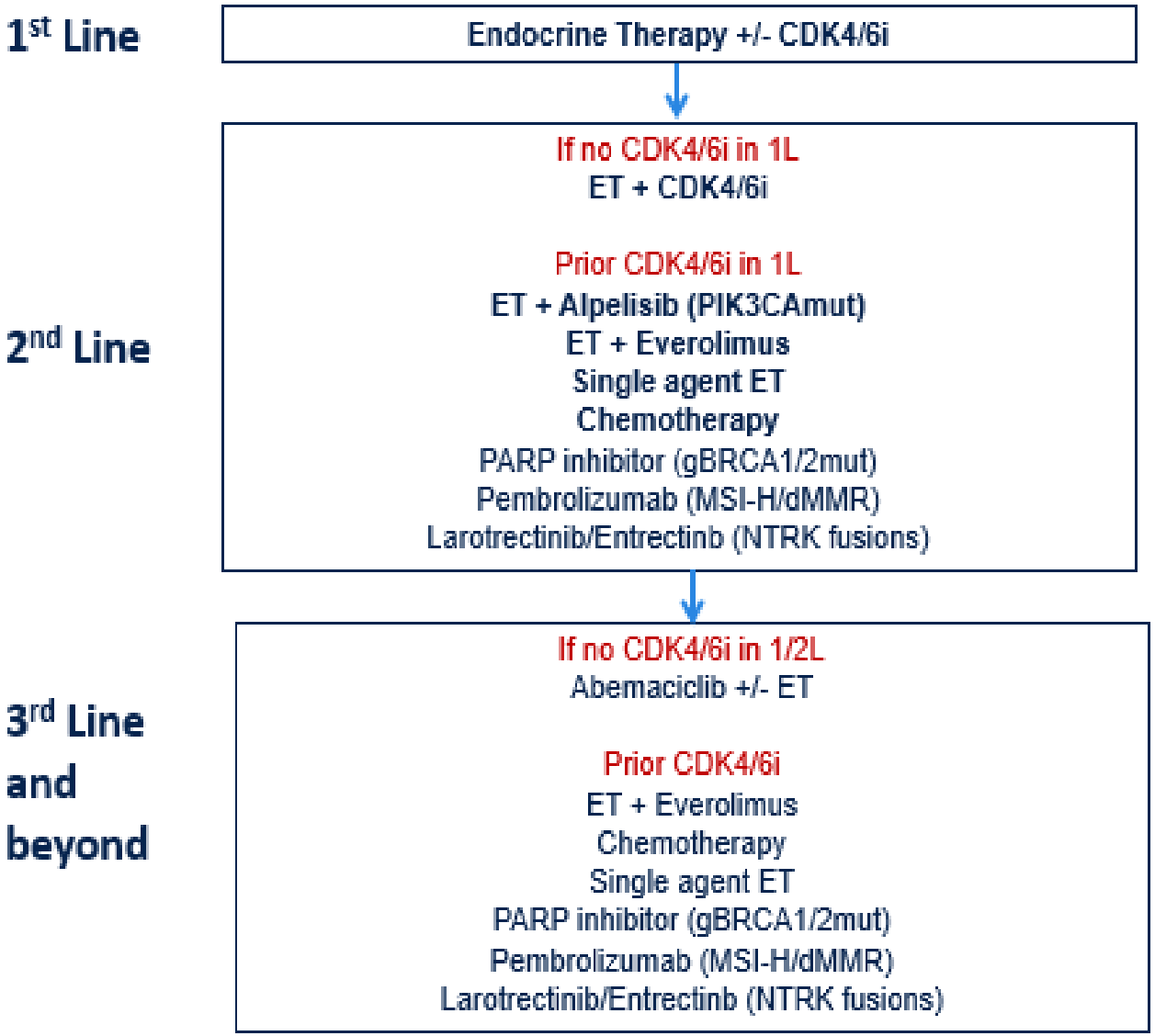
No. of Patients Still at Risk (Events)

SG	142 (0)	132 (9)	116 (24)	102 (37)	86 (53)	61 (73)	42 (83)	28 (90)	16 (96)	10 (98)	2 (99)	1 (99)	0 (99)
TPC	128 (0)	117 (8)	89 (34)	78 (45)	55 (68)	41 (79)	32 (80)	22 (83)	9 (86)	4 (87)	1 (87)	0 (88)	

OS benefit with SG over TPC observed in subgroups with Trop-2 H-score <100 and ≥100

Hazard ratio is from an unstratified Cox Regression analysis.
H-score; histochemical score; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen 2.

Clinical pathway for treatment of ER+/HER2- MBC



If ESR1 mutation: single agent elacestrant
Switch ET + Ribo if prior Palbo. No palbo after palbo

Sacituzumab if at least 2 prior lines of systemic tx
? ADC after ADC

Adapted from http://www.nccn.org/professionals/physician_gls/pdf/breast.pdfJM

Trials in HR+/HER2- MBC at Winship

- Serena-6
- Inavolisib Front line or Second Line Trial
- Loxo PI3K mutant specific inhibitor (H1047R)
- Elevate (Elacestrant combinations)
- OP-1250 Phase III Trial
- ELAINE-3 Trial
- Saci +/- Pembro

Take Home

- **Consider single agent elecestrant for those with durable response on CDK4/6i and *ESR1*m**
- **Activity of 1st line ET + ribo front vs chemotherapy in pts with ”aggressive disease”**
- **Await results from postMONARCH in terms of switching ET and CDK 4/6 inh**
- **Capivasertib might be the new SOC for all comers but toxicity remains an issue**
- **Sacituzumab Govitecan is approved for ET-resistant HR+/HER2- disease. Prior exposure to ET and at least 2 lines of systemic tx**