Update on ER+ Breast Cancer

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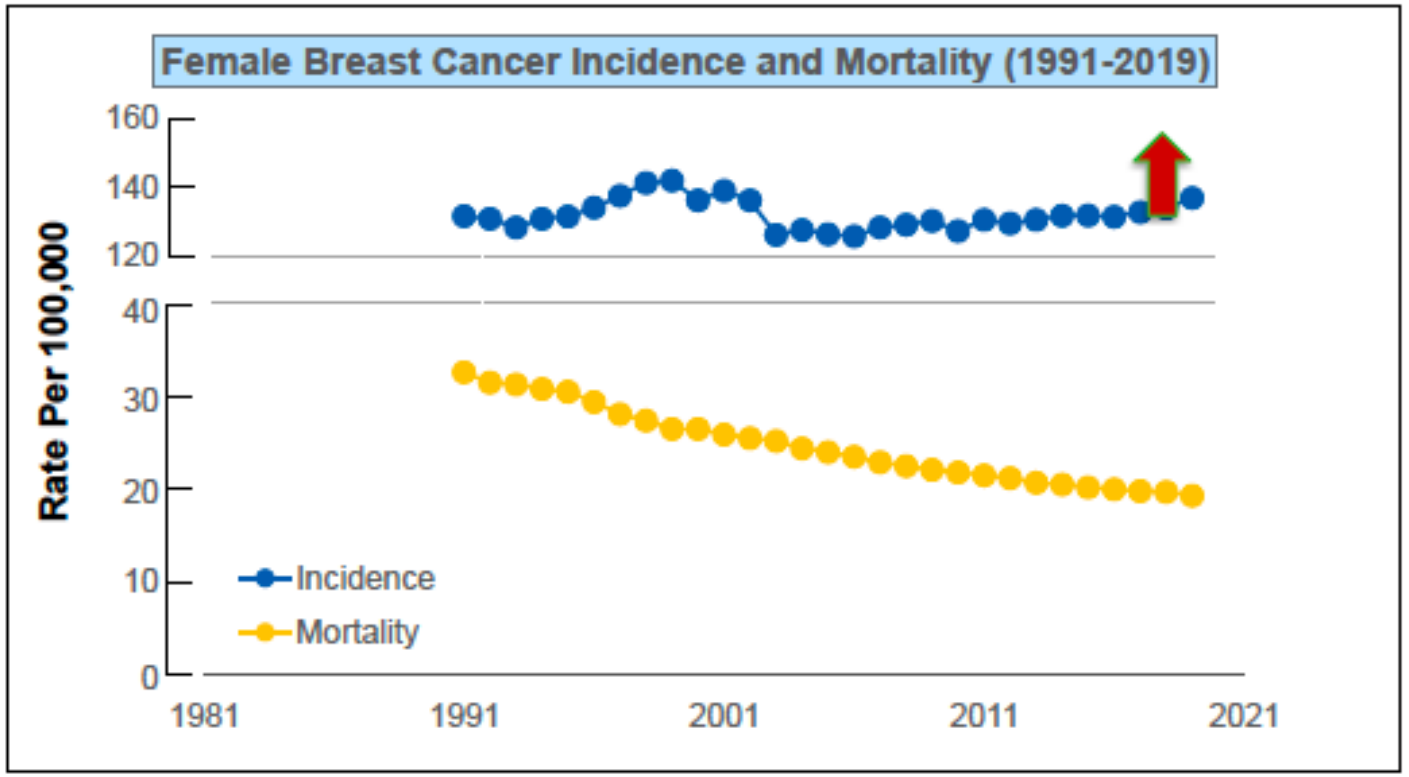
OVERALL FEMALE BREAST CANCER STATISTICS



Ref (1)

Estimated New Breast Cancer Cases (2020)

253,465

42,617

2,261,419

684,996

Estimated New Breast Cancer Deaths (2020)

Ref (2)

San Antonio Breast Cancer Symposium®, December 6-10, 2022

EARLY-ONSET BREAST CANCER IS ON THE RISE IN U.S. AND WORLDWIDE

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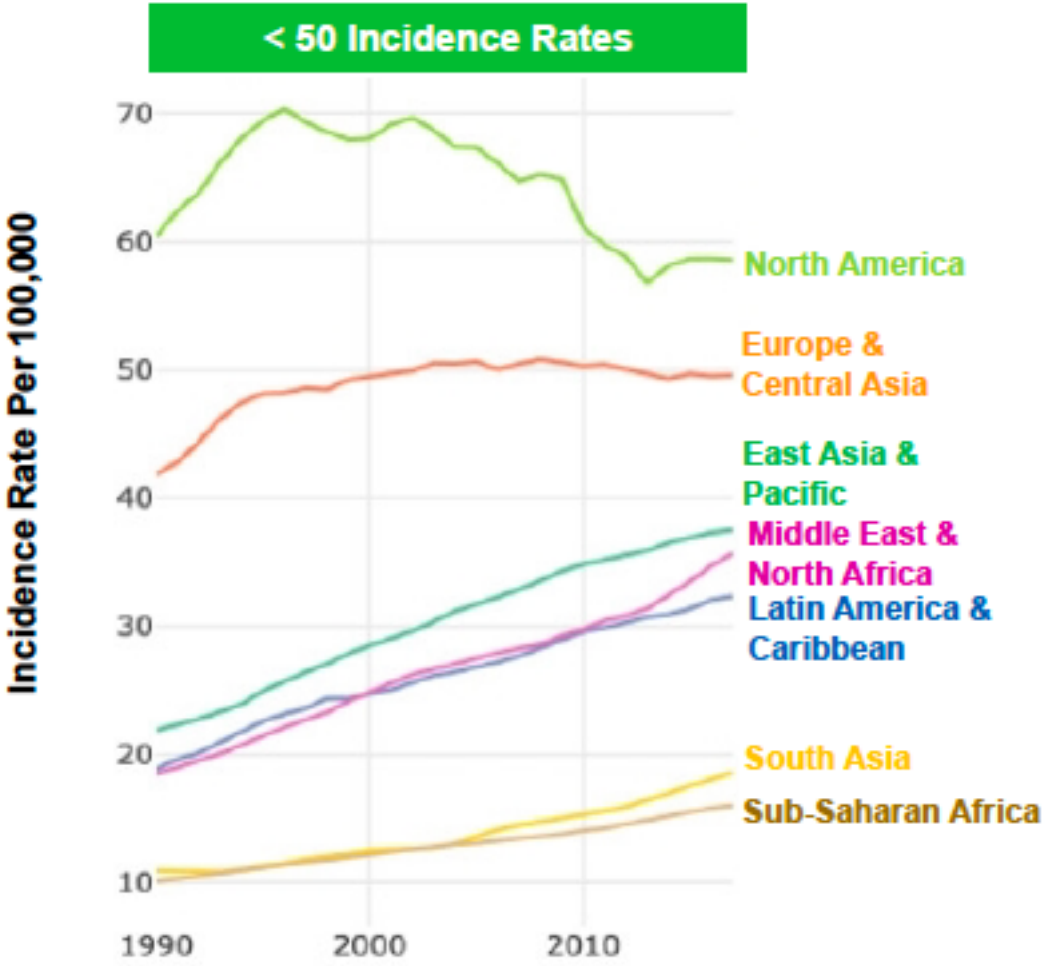
UNITED STATES

Age	Average Annual Percent Change (AAPC) Estimates					
	Year Range	AAPC (%)	Lower 95% C.I.	Upper 95% C.I.	P-Value	Direction
Ages < 50	2010-2019	1.0	0.4	1.7	<0.01	↑ Rising
	2015-2019	**1.9**	**0.4**	**3.4**	**0.01**	↑ Rising
Ages 50-64	2010-2019	0.3	-0.0	0.5	0.07	Not Significant
	2015-2019	0.3	-0.0	0.5	0.07	Not Significant
Ages 65+	2010-2019	0.5	0.4	0.6	<0.01	↑ Rising
	2015-2019	**0.5**	**0.4**	**0.6**	**<0.01**	↑ Rising

WORLDWIDE



San Antonio Breast Cancer Symposium®, December 6-10, 2022

CLINICAL TRIALS PROCESS & INNOVATION: FDA APPROVAL OF 20 NEW THERAPEUTICS AGAINST BREAST CANCER OVER THE LAST DECADE

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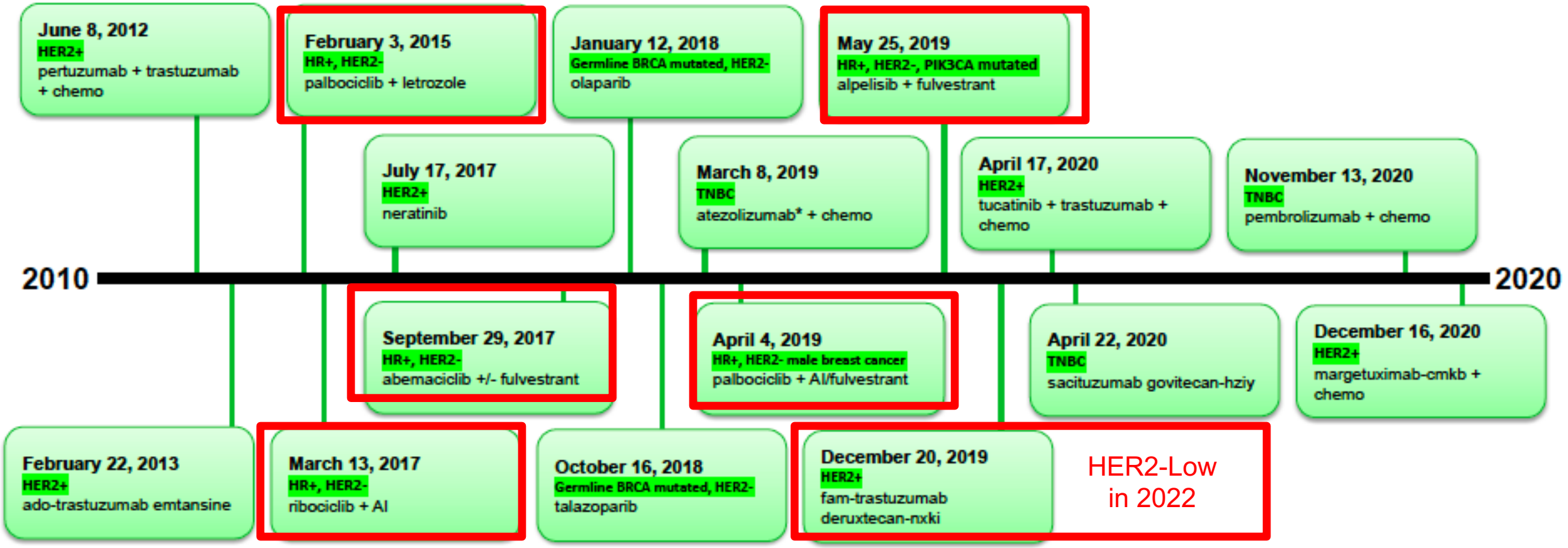
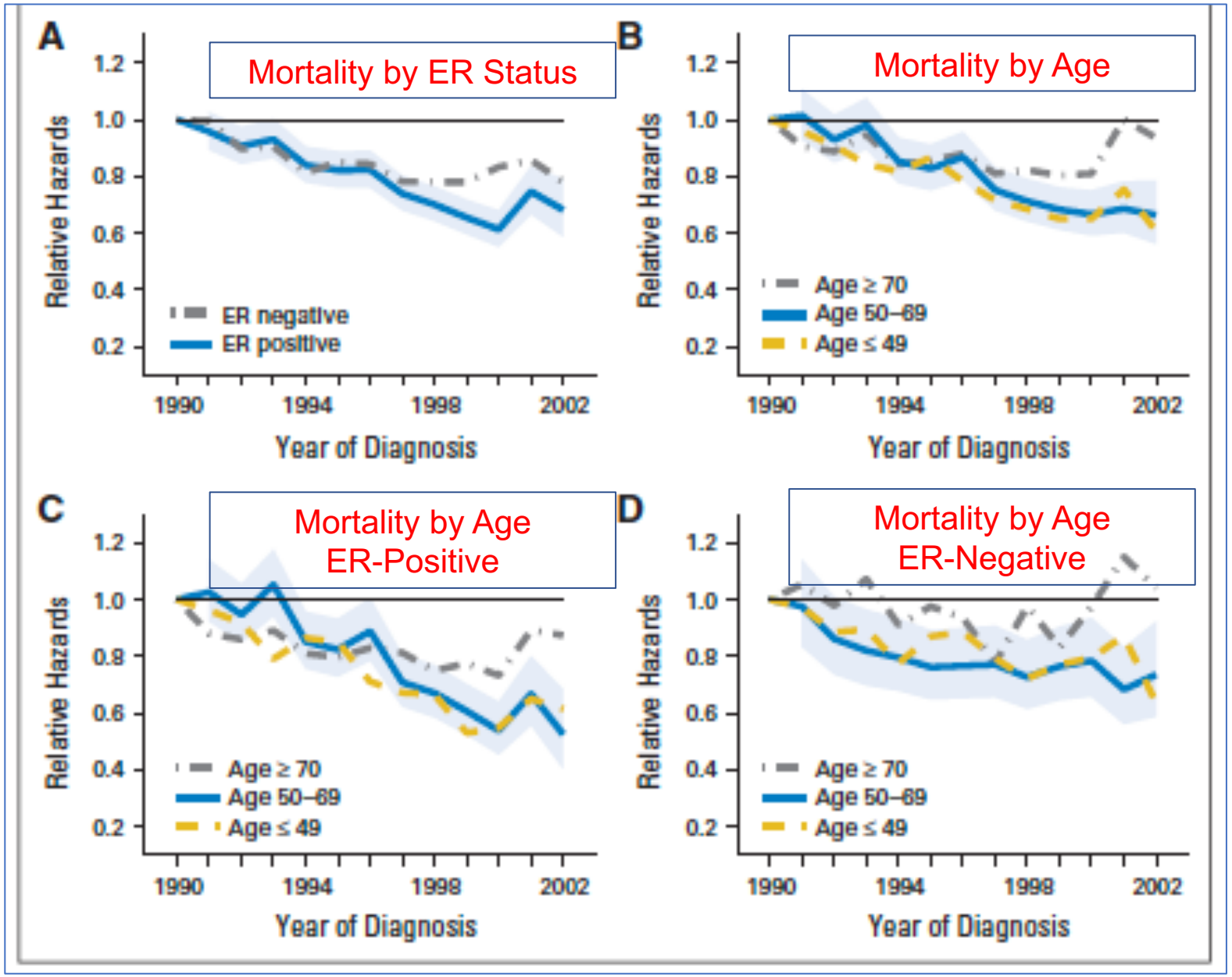


Site agnostic approvals

- 2017: pembrolizumab, MSI-h/ dMMR
- 2018: •larotrectinib, •NTRK fusion
- 2019: •entrectinib, •NTRK fusion
- 2020: •pembrolizumab, •TMB-h
- 2021: •dostarlimab, •dMMR

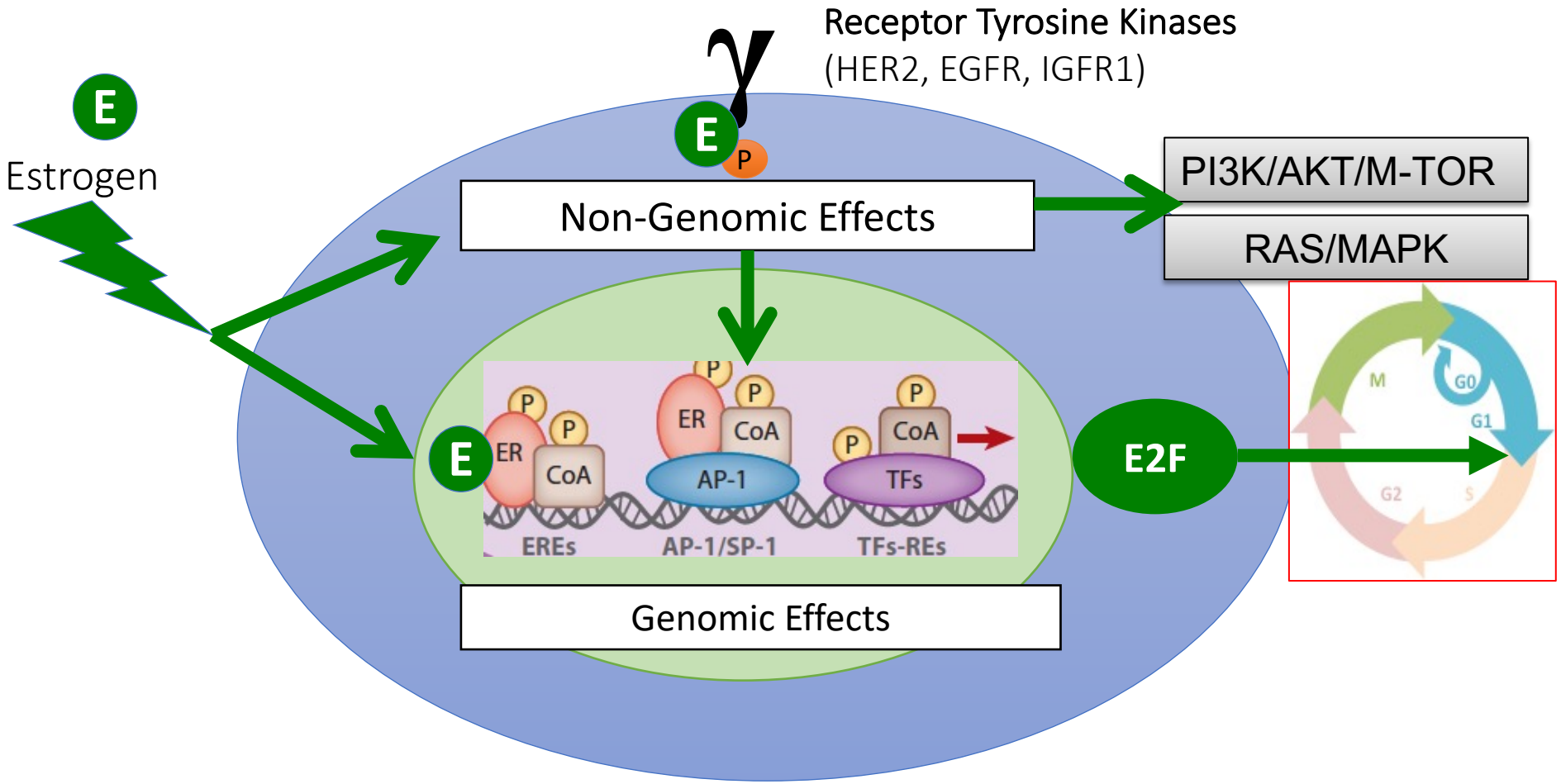
Breast Cancer Mortality Trends in the United States According to Estrogen Receptor Status and Age at Diagnosis



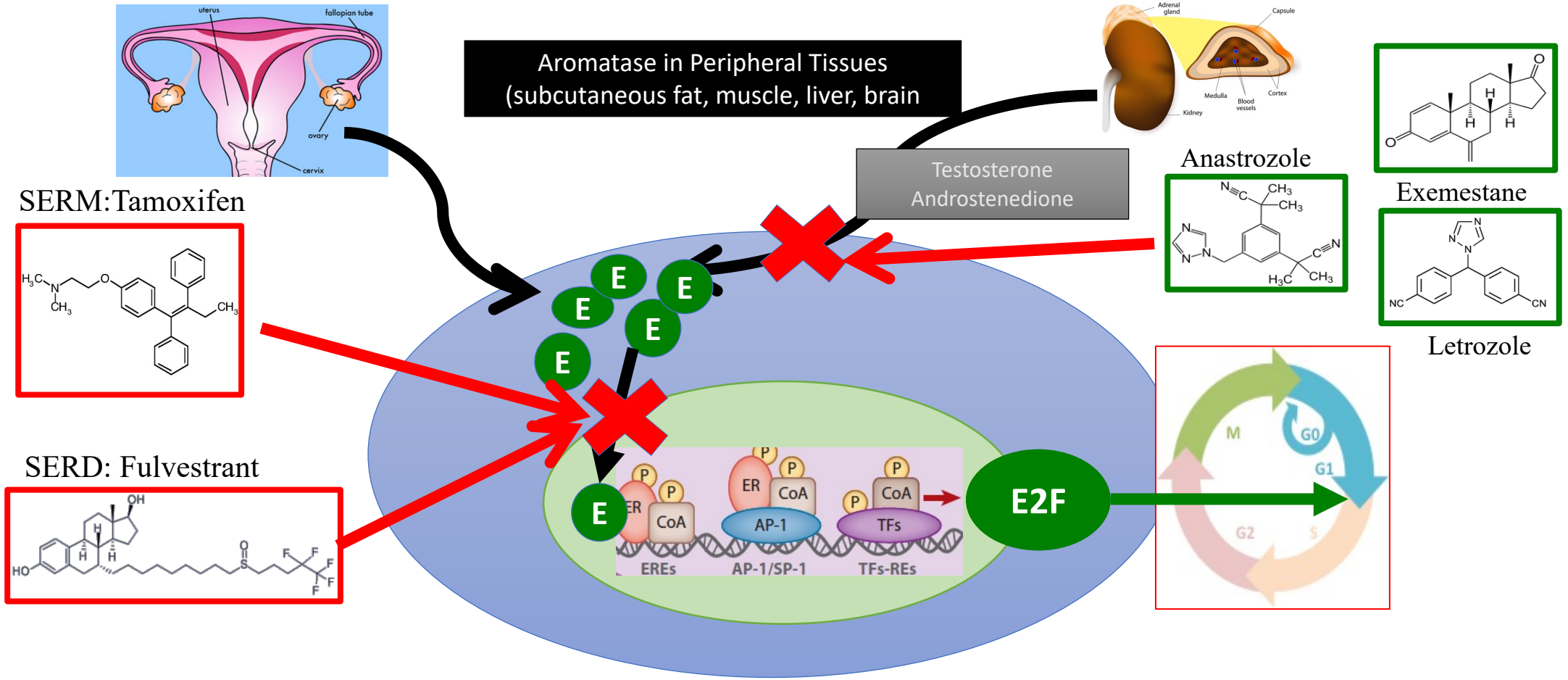
- Screening
- Adjuvant systemic therapy
  - Endocrine therapy
  - Chemotherapy
  - Anti-HER2 therapy

Jatoi et al. J Clin Oncol 2016 (PMID: 17404367)

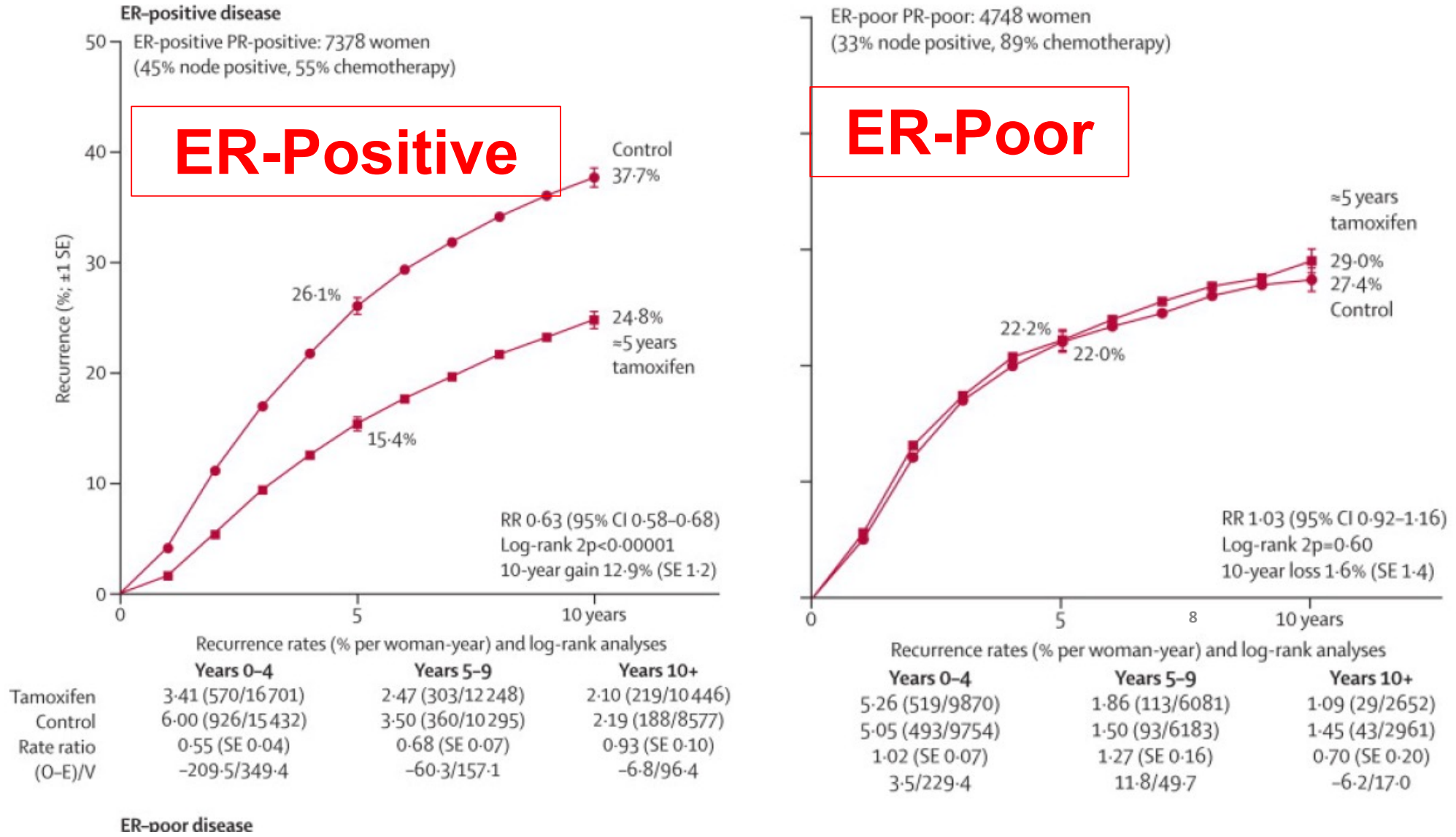
Driver and Escape Mechanisms in ER-Positive Breast Cancer



Antiestrogen Therapy

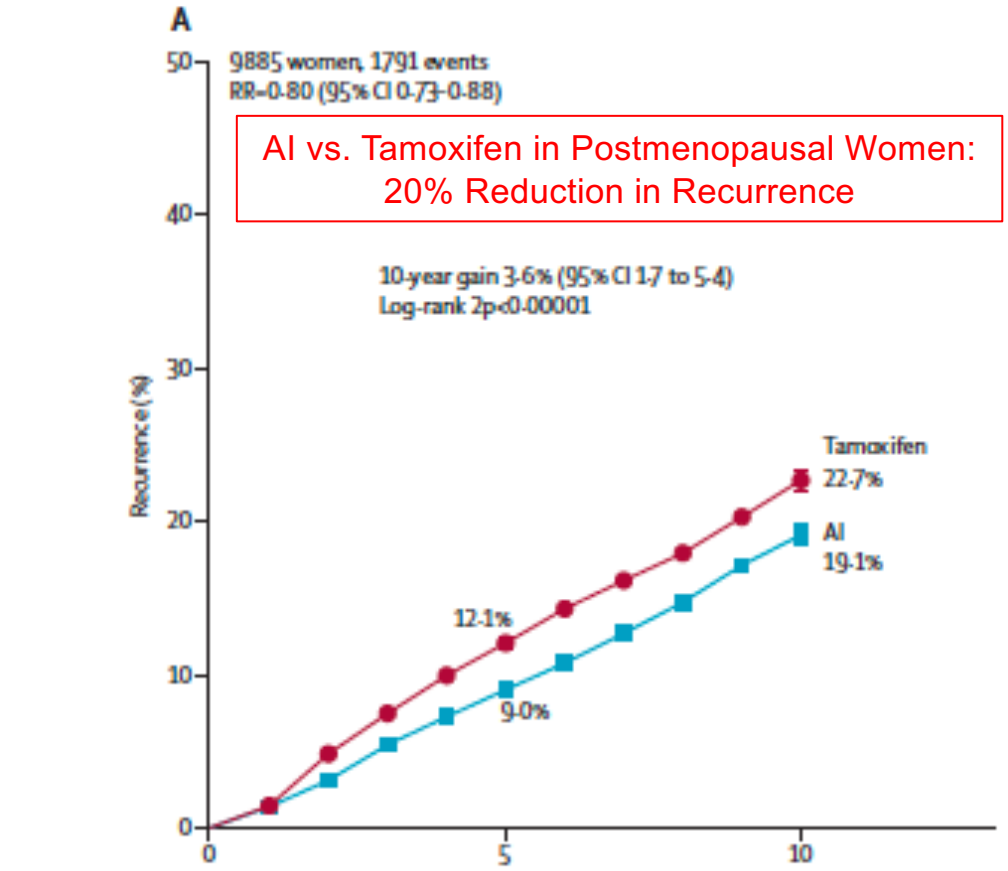


Adjuvant Endocrine Therapy in ER-Positive Early Breast Cancer



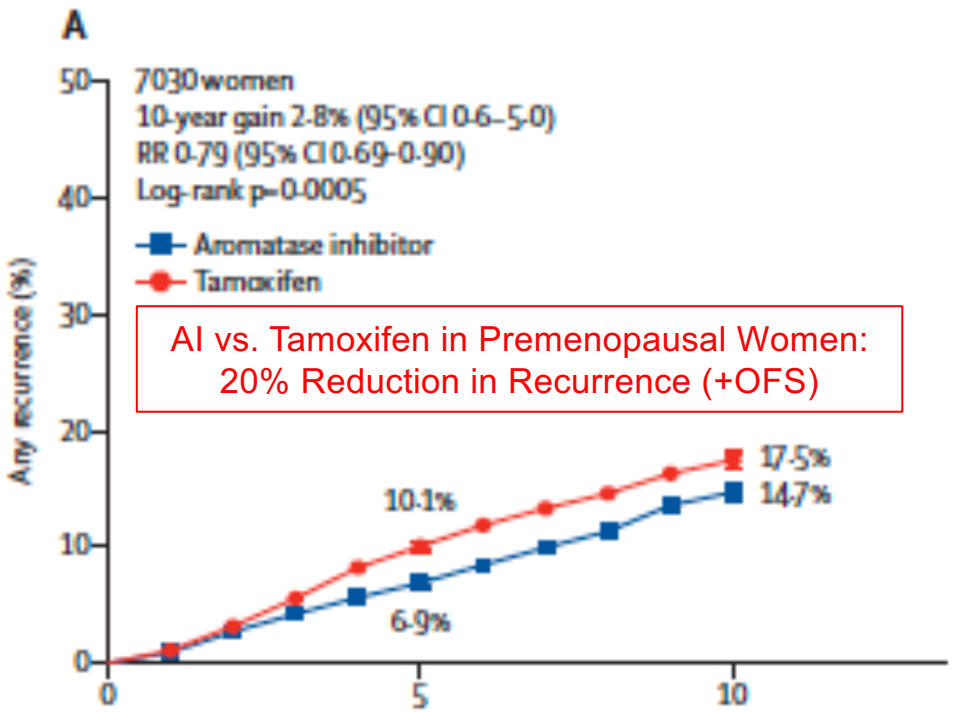
Early Breast Cancer Trialists' Collaborative Group. Lancet 2011:378; 771 (PMID: 21802721)

Complete Estrogen Deprivation in Post and Premenopausal Women Compared with Tamoxifen (SERM)



Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–1	Years 2–4	Years 5–9	Year 10+
AI	1·62 (157/9691)	2·14 (285/13 336)	2·33 (365/15 648)	3·23 (20/619)
Tamoxifen	2·41 (230/9542)	2·62 (338/12 906)	2·48 (372/14 985)	4·54 (24/529)
Rate ratio (95% CI)	0·64 (0·52–0·78)	0·80 (0·68–0·93)	0·92 (0·79–1·06)	0·72 (0·39–1·30)
from (O-E)/V	−41·1/92·8	−34·1/149·0	−15·5/177·2	−3·6/10·7



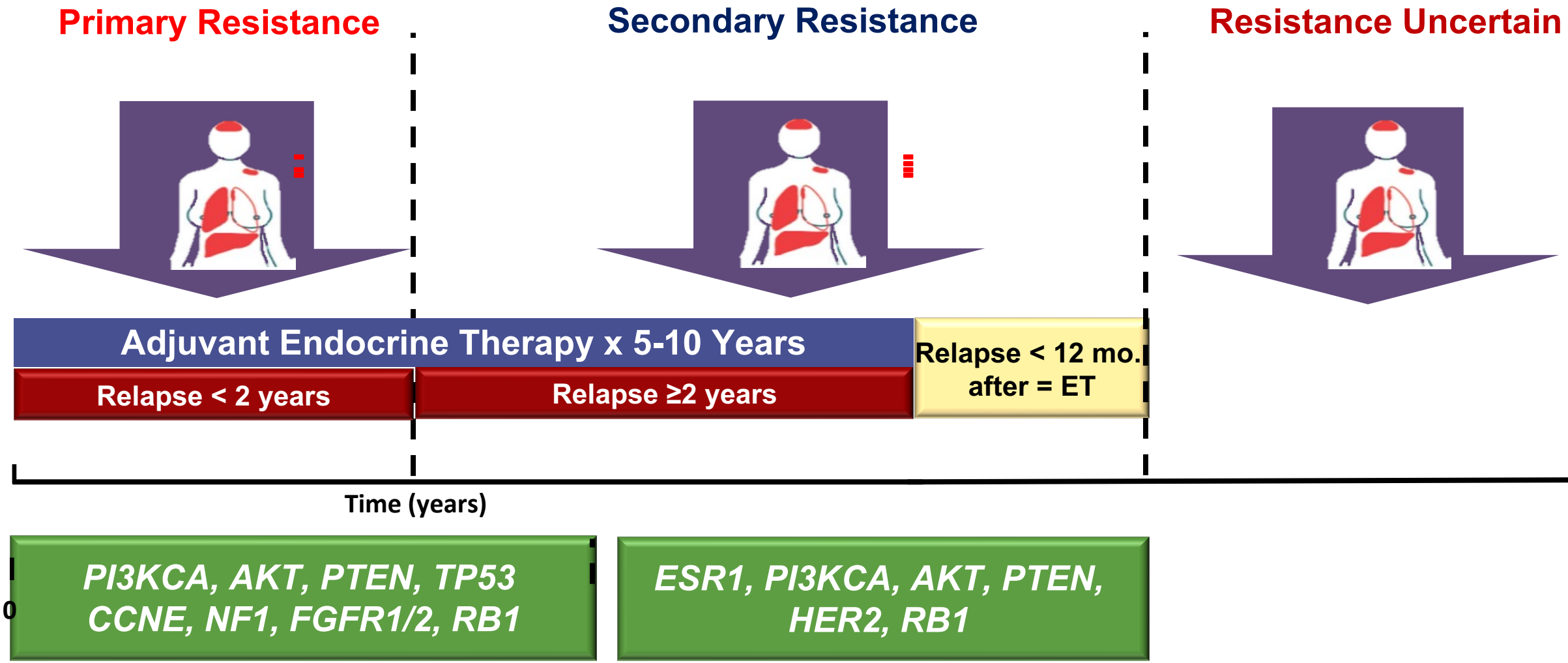
Recurrence rates per year (% [events/women-years]) and log-rank analyses

	Years 0–4	Years 5–9	Years ≥ 10
Aromatase inhibitor	1·46 (237/16 276)	1·76 (158/8999)	1·89 (9/476)
Tamoxifen	2·08 (332/15 958)	1·74 (150/8639)	0·44 (2/459)
RR (95% CI)	0·68 (0·58–0·80)	0·98 (0·78–1·23)	3·31 (0·99–11·06)
from (o–e)/v	−52·9/137·2	−1·2/74·5	3·2/2·6

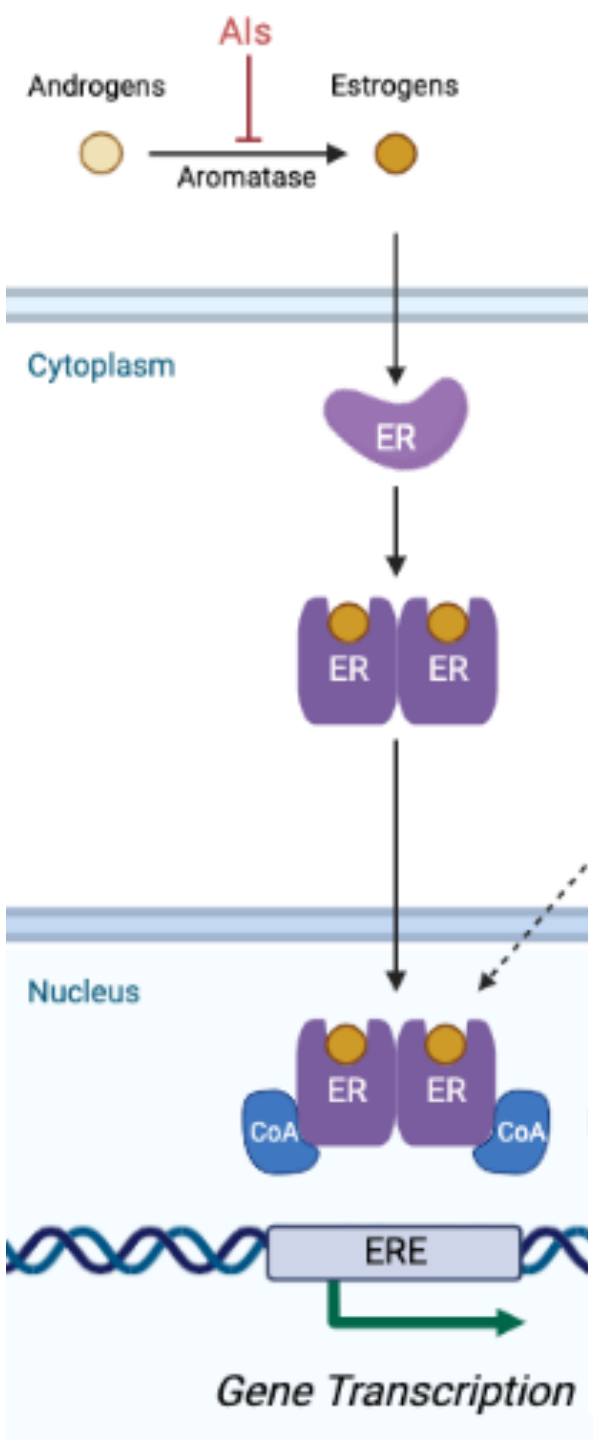
EBCTCG. Lancet 2015 (PMID: 26211827)

EBCTCG. Lancet Oncology 2022 (PMID: 35123662

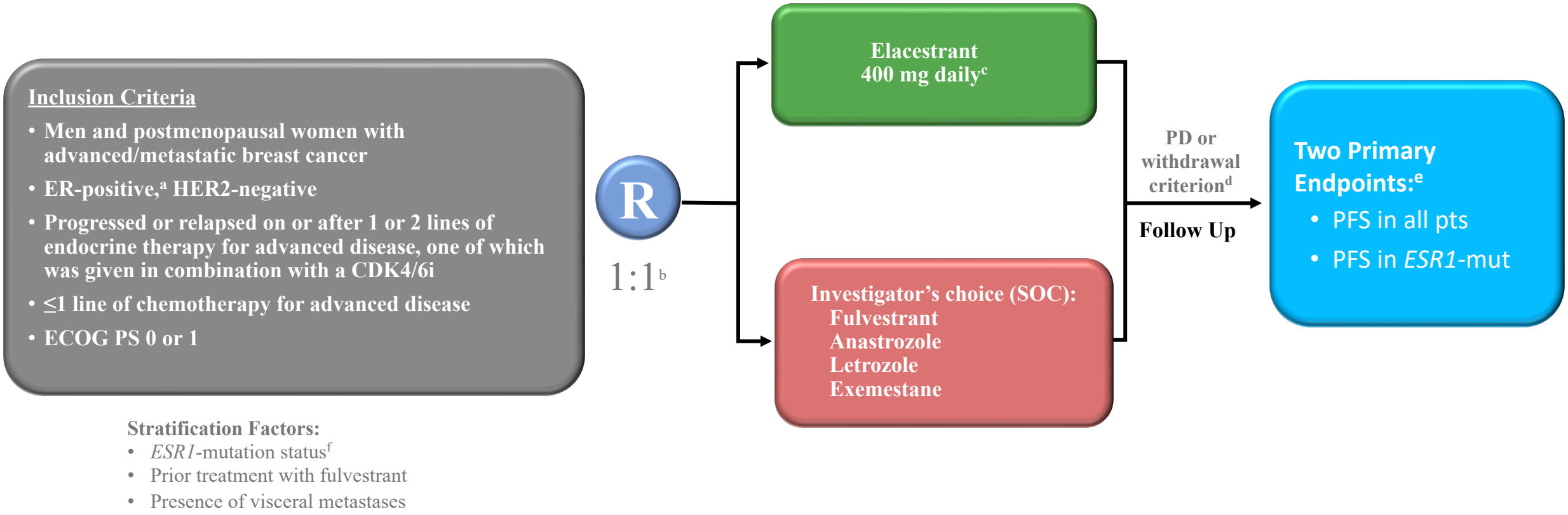
Resistance to Endocrine Therapy:
Definitions and Molecular Mechanisms



Created from: Cardoso F, et al. *Ann Oncol.* 2018;29:1634-1657.


AIs
Androgens
Estrogens
Aromatase
Cytoplasm
ER
ER
ER
Nucleus
ER
ER
CoA
CoA
ERE
Gene Transcription

EMERALD Phase 3 Study Design

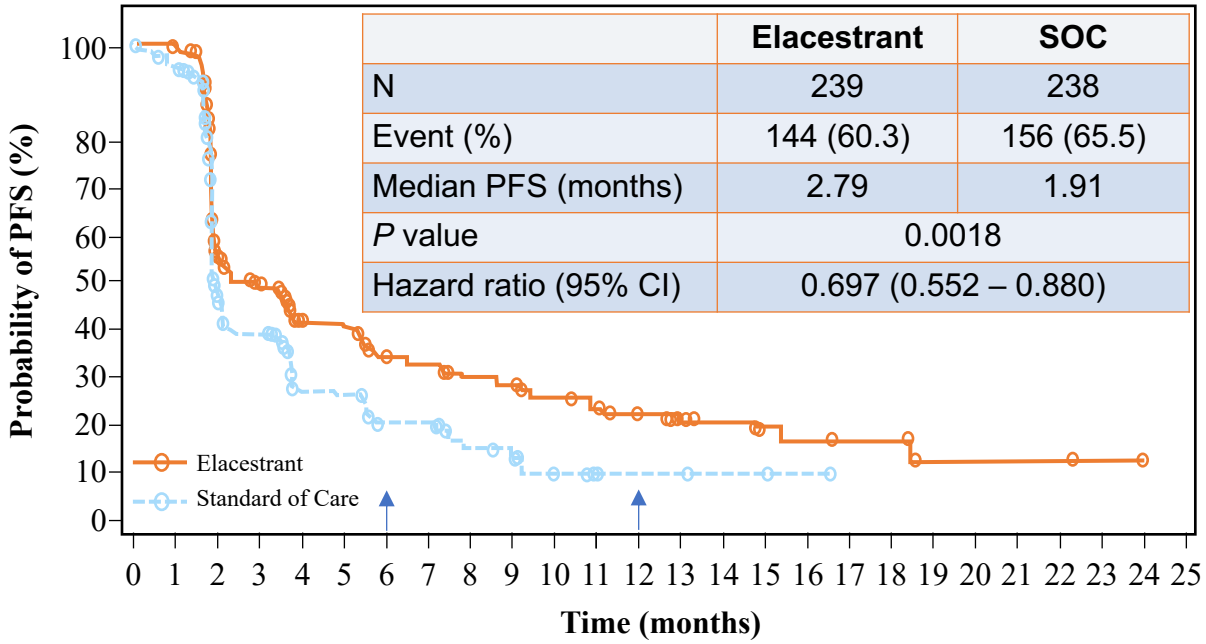


[a]Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry; [b]Recruitment from February 2019 to October 2020; [c]Protocol-defined dose reductions permitted; [d]Restaging CT scans every 8 weeks; [e]Blinded Independent Central Review; [f]*ESR1*-mutation status was determined by ctDNA analysis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

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

Median PFS & PFS Rate at 12 Months: All Patients and *mESR1* Group

All Patients

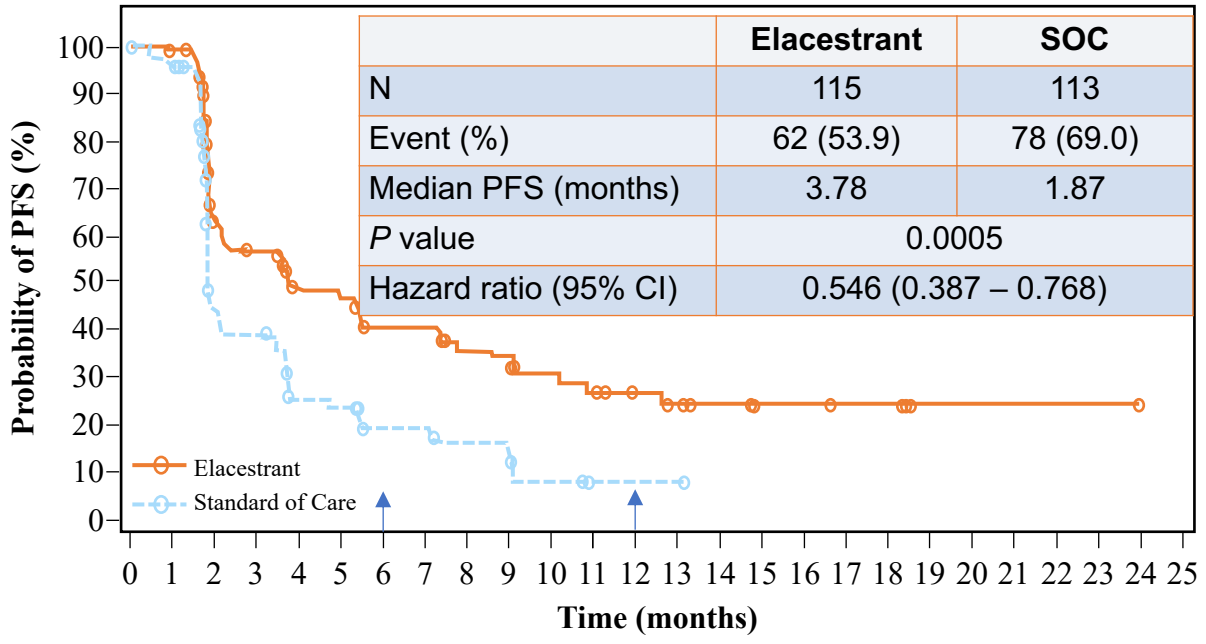


	Elacestrant	SOC
N	239	238
Event (%)	144 (60.3)	156 (65.5)
Median PFS (months)	2.79	1.91
P value	0.0018	
Hazard ratio (95% CI)	0.697 (0.552 – 0.880)	

Elacestrant	239	223	106	89	60	57	42	40	34	33	27	24	19	13	11	8	7	6	6	2	2	2	2	1	0
SOC	238	206	84	68	39	38	25	25	16	15	7	4	3	3	2	2	1	0							

	Elacestrant	SOC
N	239	238
PFS rate at 6 months (95% CI)	34.3% (27.2%-41.5%)	20.4% (14.1-26.7%)
PFS rate at 12 months (95% CI)	22.3% (15.2%-29.4%)	9.4% (4.0%-14.8%)

Only Tumors Harboring *mESR1*



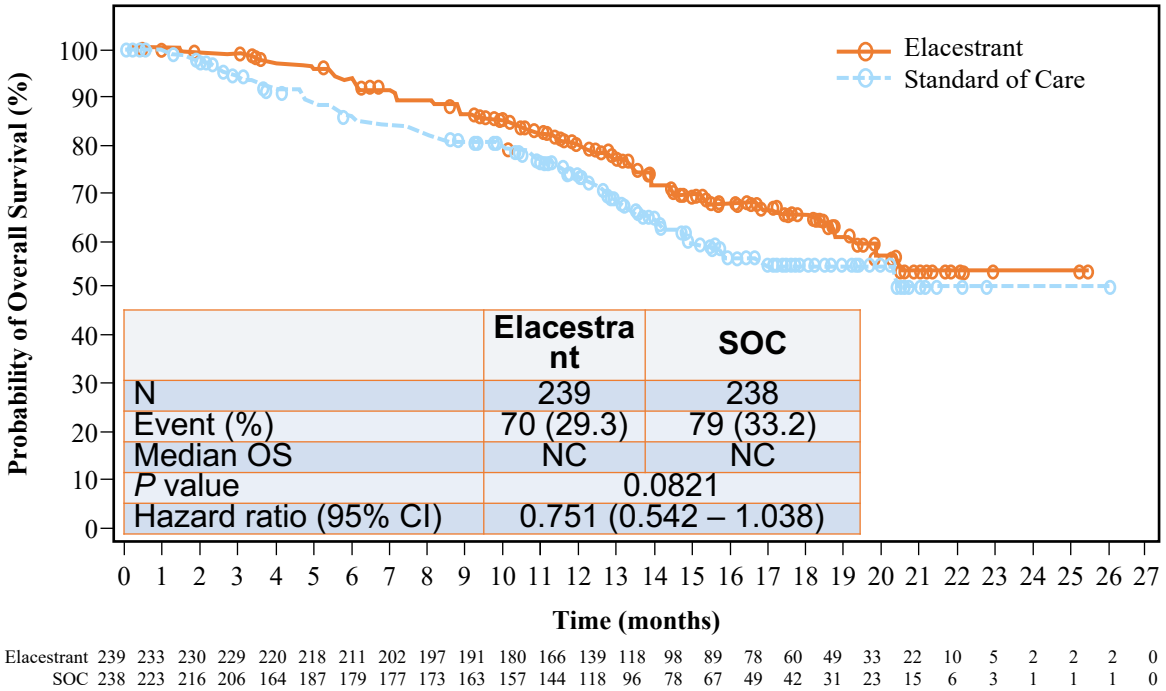
	Elacestrant	SOC
N	115	113
Event (%)	62 (53.9)	78 (69.0)
Median PFS (months)	3.78	1.87
P value	0.0005	
Hazard ratio (95% CI)	0.546 (0.387 – 0.768)	

Elacestrant	115	105	54	46	35	33	26	26	21	20	16	14	11	9	7	5	5	4	4	1	1	1	1	1	0
SOC	113	99	39	34	19	18	12	12	9	9	4	1	1	1	0										

	Elacestrant	SOC
N	115	113
PFS rate at 6 months (95% CI)	40.8% (30.1%-51.4%)	19.1% (14.1-26.7%)
PFS rate at 12 months (95% CI)	26.8% (16.2%-37.4%)	8.2% (1.3%-15.1%)

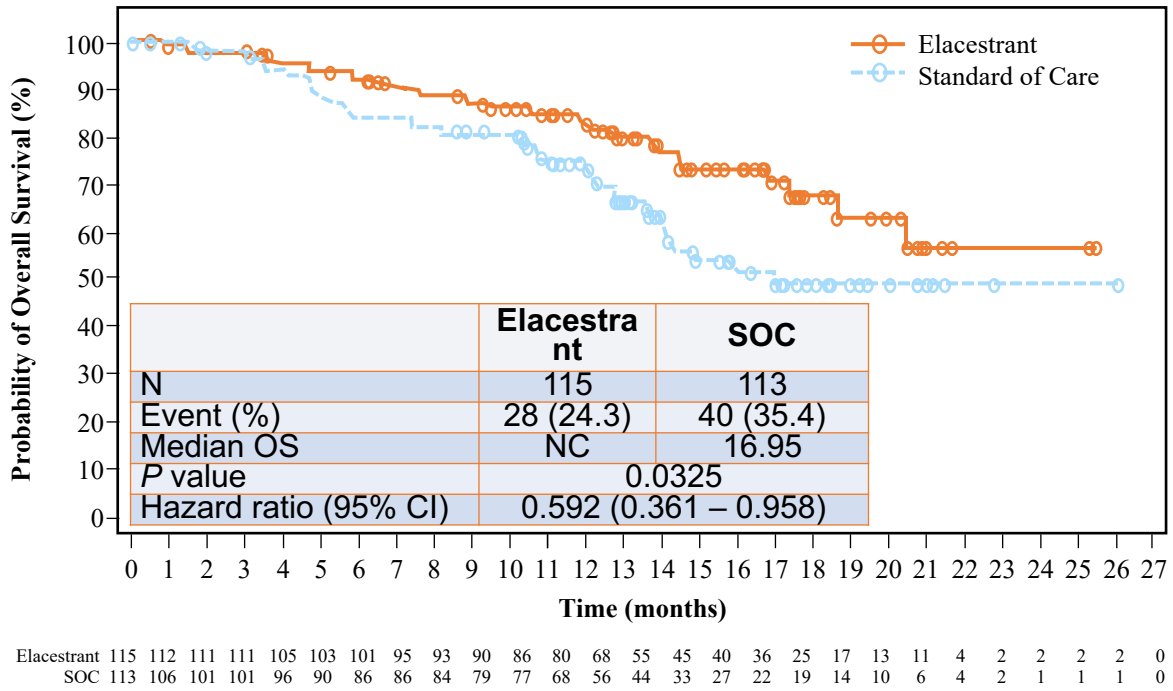
Overall Survival (Interim Analysis)

All Patients



	Elacestrant	SOC
N	239	238
Event (%)	70 (29.3)	79 (33.2)
Median OS	NC	NC
P value	0.0821	
Hazard ratio (95% CI)	0.751 (0.542 – 1.038)	

Patients with *mESR1*



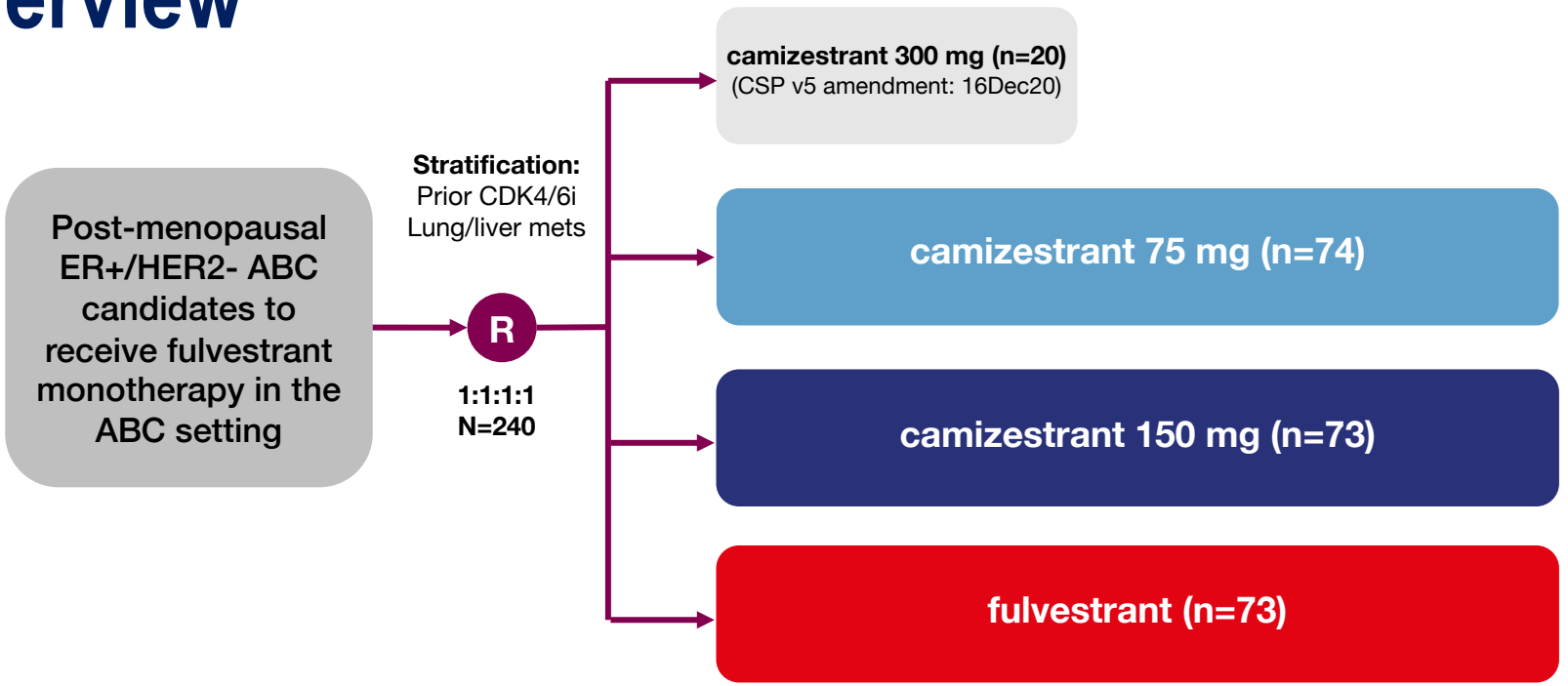
	Elacestrant	SOC
N	115	113
Event (%)	28 (24.3)	40 (35.4)
Median OS	NC	16.95
P value	0.0325	
Hazard ratio (95% CI)	0.592 (0.361 – 0.958)	

- While no statistically significant differences were noted at the α=0.0001 level in OS, an evident trend favoring elacestrant over SOC was noted in both groups. Final analysis is expected to take place in late 2022/early 2023.

SERENA-2 study overview

Key inclusion/exclusion criteria:

- Recurrence or progression on at least one line of ET
- No prior fulvestrant or oral SERD in ABC
- No more than one line of ET in ABC setting
- No more than one line CT in ABC setting
- Measurable and non-measurable disease

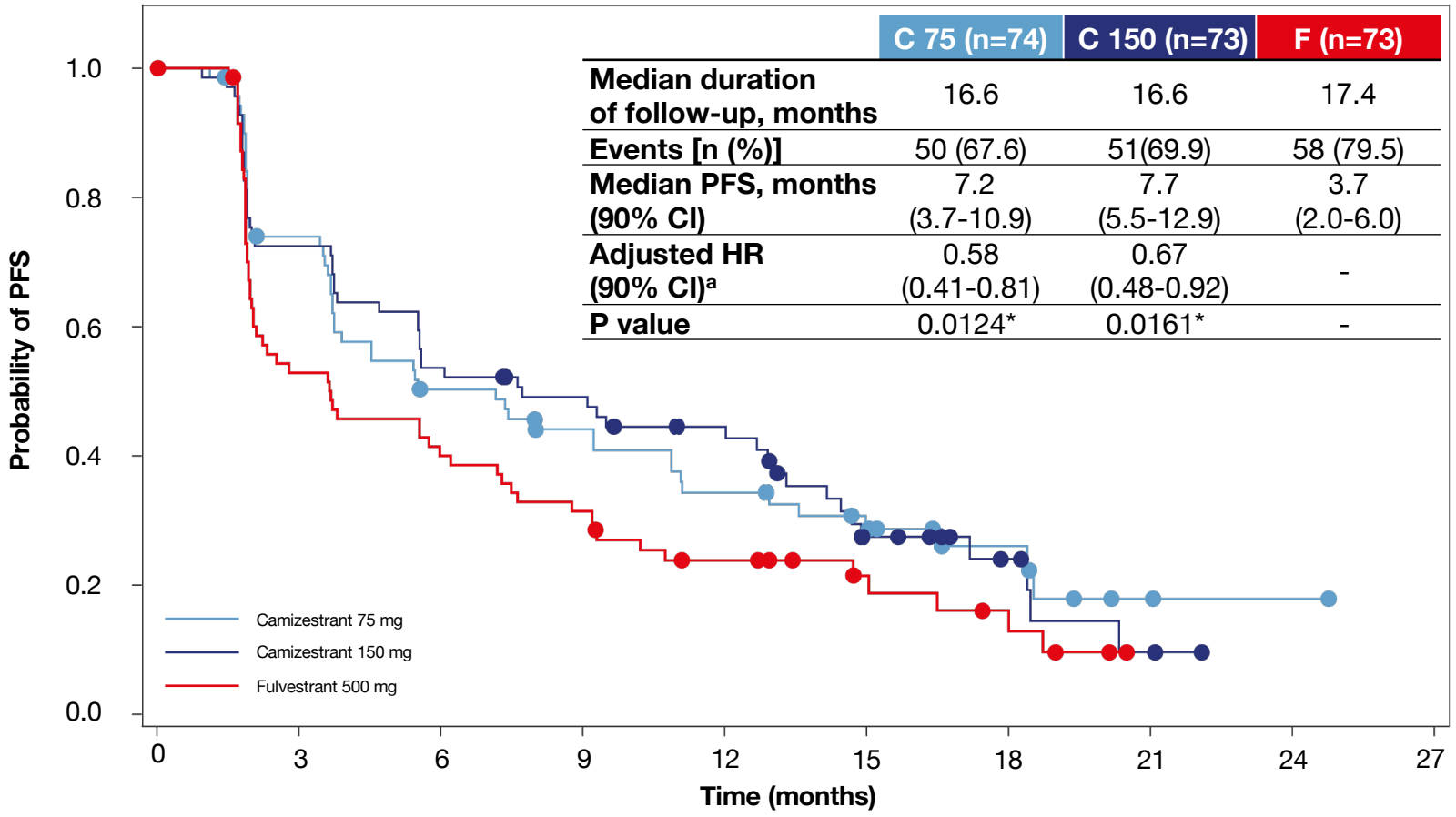


- **Primary endpoint:** PFS (investigator assessment*)
- **Secondary endpoints:** CBR24, ORR, OS, safety
- **Translational endpoints:** serial ctDNA analysis including *ESR1*m, serial CTCs analysis

*disease progression assessed by the Investigator and defined using RECIST, version 1.1

ABC: advanced breast cancer; CBR24: clinical benefit rate at 24 weeks; CDK4/6i: CDK4/6 inhibitor; CT: chemotherapy; CTC: circulating tumor cells; ctDNA: circulating tumor DNA; ER: estrogen receptor; *ESR1*m: mutation in estrogen receptor 1 gene; ET: endocrine therapy; HER2: human epidermal growth factor; PFS: progression-free survival; R: randomization; RECIST: Response Evaluation Criteria for Solid Tumors; SERD: selective estrogen receptor degrader

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*	-

C 75	74	50	33	27	21	14	7	2	1	0
C 150	73	50	37	32	25	12	6	2	0	
F	73	37	28	22	14	8	5	0		

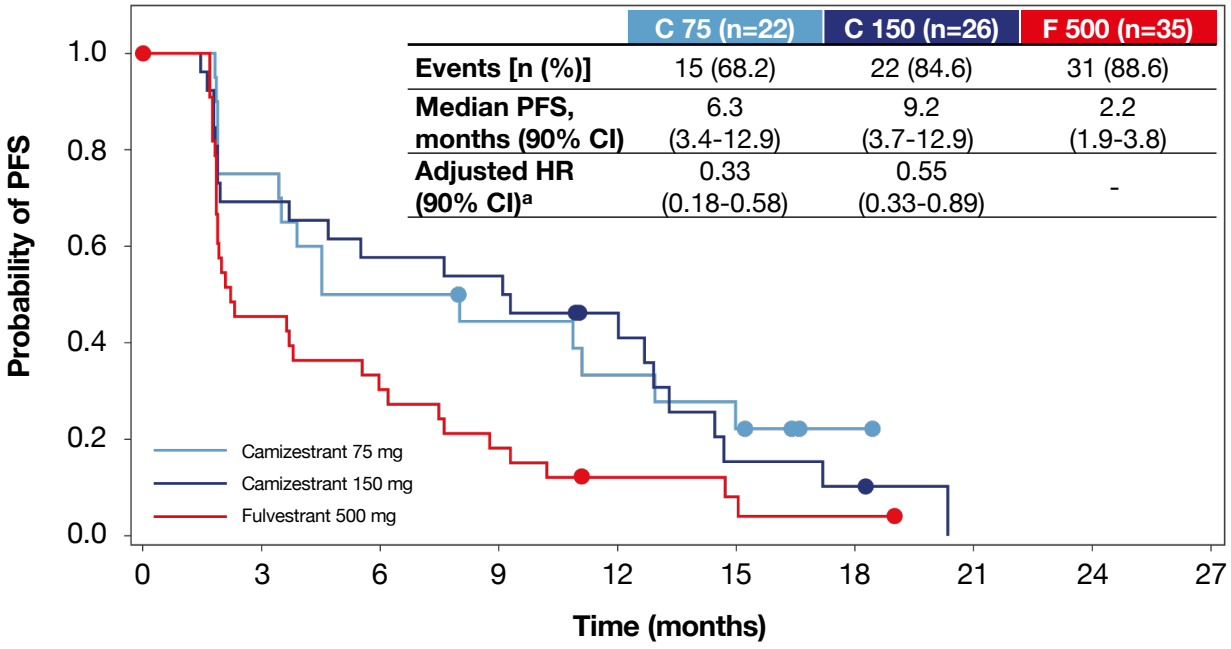
*Statistically significant; [a]HRs adjusted for prior use of CDK4/6i and liver/lung metastases

CDK4/6i: CDK4/6 inhibitor; CI: confidence interval; HR: hazard ratio; PFS: progression-free survival

In the overall population, camizestrant produces a statistically significant and clinically meaningful improvement in PFS for both 75 and 150 mg camizestrant doses over fulvestrant

PFS in patients by detectable *ESR1*m

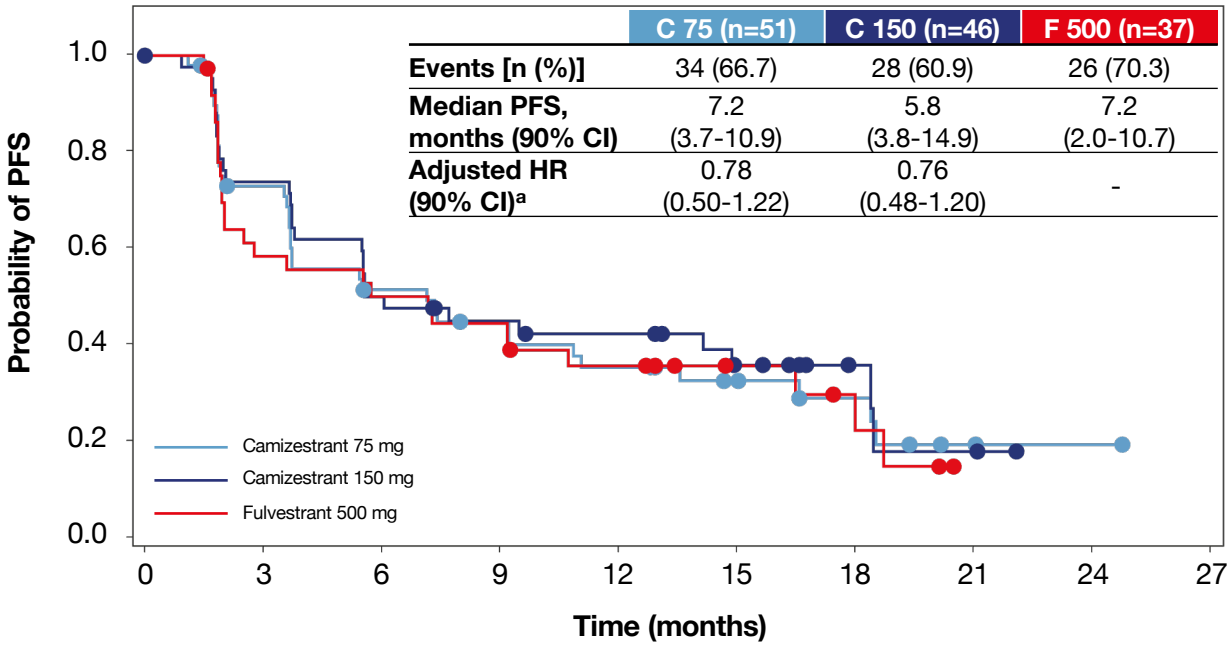
*ESR1*m detectable at baseline



	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	

- In the sub-population of patients with detectable *ESR1*m at baseline, camizestrant at both doses produces a clinically meaningful improvement in PFS over fulvestrant

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

CI: confidence interval; CDK4/6i: CDK4/6 inhibitor; ESR1m: mutation in estrogen receptor 1 gene; HR: hazard ratio; PFS: progression-free survival

ARV-471, a PROTAC estrogen receptor (ER) degrader in advanced ER-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer: phase 2 expansion (VERITAC) of a phase 1/2 study

Sara A Hurvitz,[1] **Anne F Schott**,[2] Cynthia Ma,[3] Erika P Hamilton,[4] Rita Nanda,[5] George Zahrah,[6] Natasha Hunter,[7] Antoinette R Tan,[8] Melinda L Telli,[9] Jesus Anampa Mesias,[10] Rinath Jeselsohn,[11] Pamela Munster,[12] Haolan Lu,[13] Richard Gedrich,[13] Cecile Mather,[13] Janaki Parameswaran,[13] Hyo S Han[14]

[1]UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA; [2]Rogel Cancer Center, University of Michigan Health, Ann Arbor, MI; [3]Washington University, St Louis, MO; [4]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [5]University of Chicago Medicine, Chicago, IL; [6]Norwalk Hospital, Norwalk, CT; [7]Seattle Cancer Care Alliance, Seattle, WA; [8]Levine Cancer Institute, Atrium Health, Charlotte, NC; [9]Stanford University School of Medicine, Stanford, CA; [10]Albert Einstein College of Medicine, Bronx, NY; [11]Dana-Farber Cancer Institute, Boston, MA; [12]University of California San Francisco, San Francisco, CA; [13]Arvinas Operations, Inc, New Haven, CT; [14]Moffitt Cancer Center, Tampa, FL

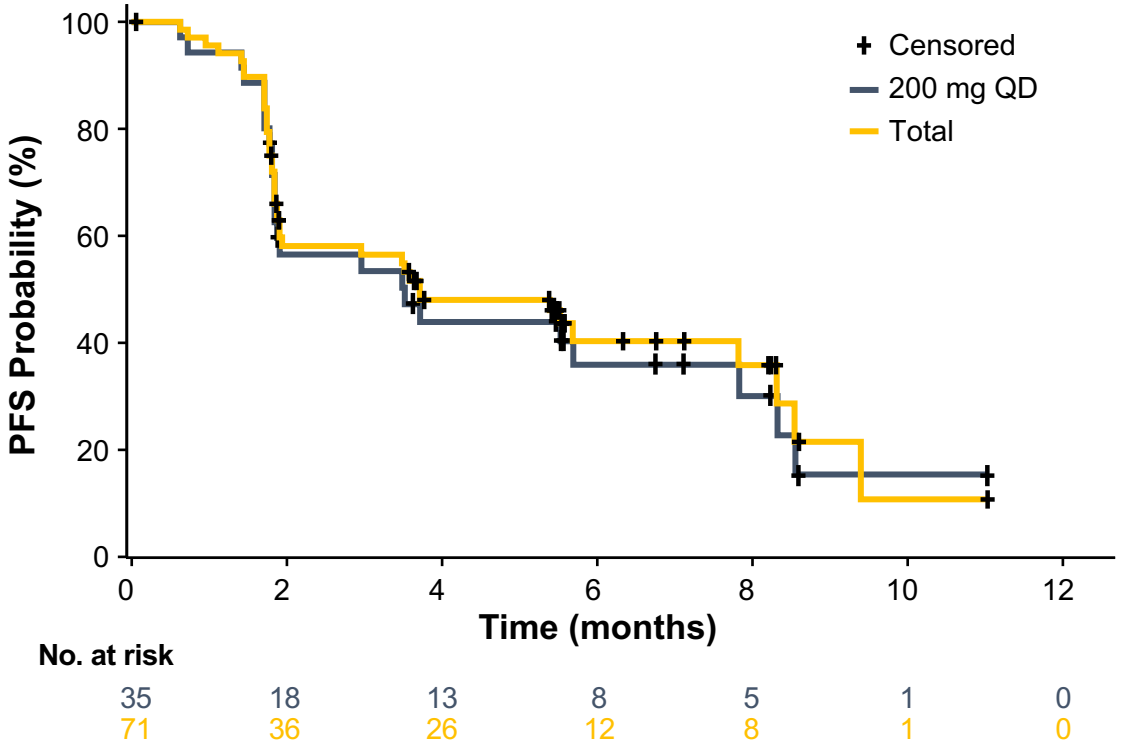
Primary Endpoint: Clinical Benefit Rate[a] (VERITAC)

	200 mg QD (n=35)	500 mg QD (n=36)	Total (N=71)
CBR, % (95% CI)	37.1 (21.5–55.1)	38.9 (23.1–56.5)	38.0 (26.8–50.3)
Patients with mutant *ESR1*	(n=19)	(n=22)	(n=41)
CBR, % (95% CI)	47.4 (24.4–71.1)	54.5 (32.2–75.6)	51.2 (35.1–67.1)

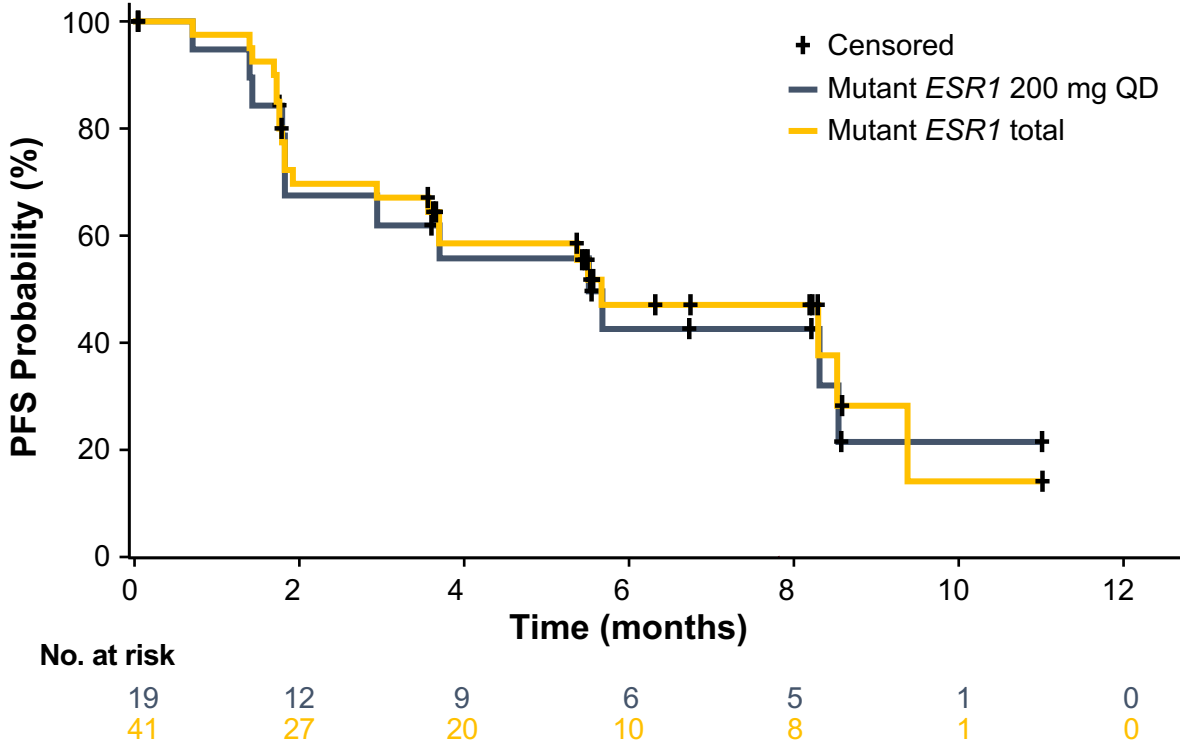
[a]Rate of confirmed complete response or partial response or stable disease ≥24 weeks
CBR=clinical benefit rate; *ESR1*=estrogen receptor 1 gene; QD=once daily

Progression-Free Survival[a] (VERITAC)

	All Patients	
	200 mg QD (n=35)	Total (N=71)
Events, n (%)	24 (68.6)	41 (57.7)
mPFS, mo (95% CI)	3.5 (1.8–7.8)	3.7 (1.9–8.3)



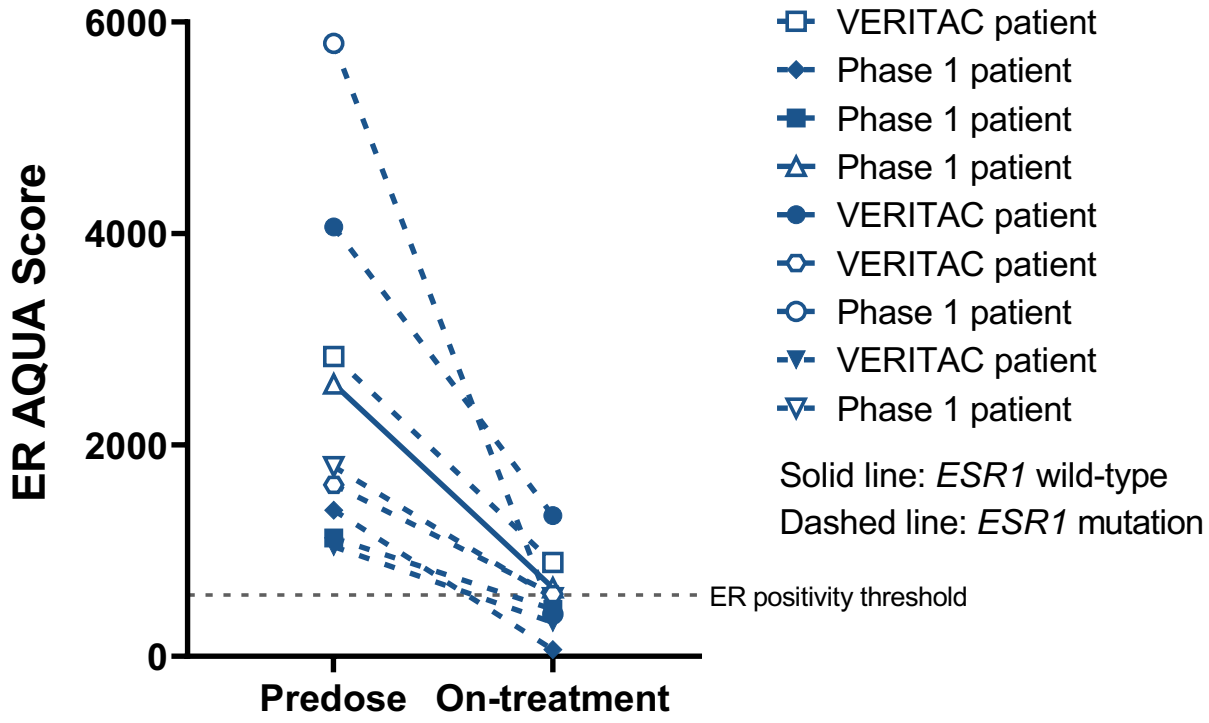
	Mutant *ESR1*	
	200 mg QD (n=19)	Total (n=41)
Events, n (%)	12 (63.2)	22 (53.7)
mPFS, mo (95% CI)	5.5 (1.8–8.5)	5.7 (3.6–9.4)



[a]Limited follow-up in 500-mg QD cohort led to ≥50% of patients censored for PFS (curve not shown)

ESR1=estrogen receptor 1 gene; mPFS=median progression-free survival; PFS=progression-free survival; QD=once daily

ER Degradation[a] With 200 mg QD ARV-471 (Phase 1/VERITAC)



- Median ER degradation was 69% (range: 28%–95%)
- Mean ER degradation was 71%

[a]ER immunoreactivity analyzed by QIF using the AQUA method, and ER positivity threshold derived by examining AQUA scores and visually inspecting all samples in the dataset to determine a cut point for ER positivity; *ESR1* mutation status determined from tumor biopsy (n=1) or circulating tumor DNA (n=8)
AQUA=automated quantitative analysis; ER=estrogen receptor; *ESR1*=estrogen receptor 1 gene; QD=once daily; QIF=quantitative immunofluorescence

Key Druggable Pathways and/or Targets in Breast Cancer

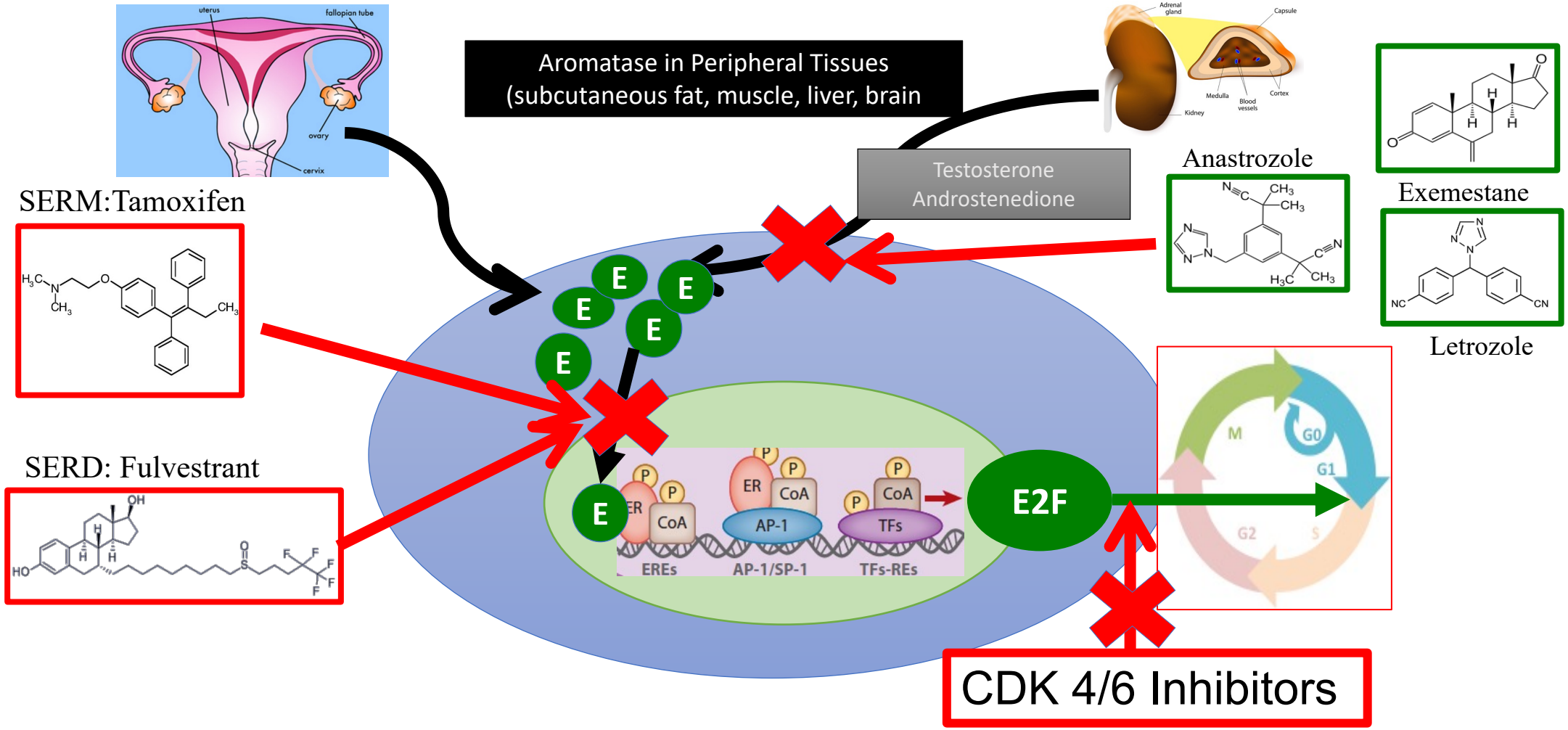
Clinical Endpoints in Metastatic Breast Caner	Objective Response	Progression-Free Survival	Overall Survival	Agents with OS Benefit	Other Agents
PATHWAY – pathway signaling disruption mediates anti-tumor effects					
✓ ER-mediated signaling	X	X	X	Tamoxifen Aromatase inhibitors	SERDs
✓ CDK4/6-mediated signaling	X	X	X	Ribociclib Abemaciclib	Palbociclib
✓ PI3K/AKT/mTOR signaling	X	X			Alpelisib Everolimus
✓ Immune checkpoints	X	X	X	Pembrolizumab	
✓ DNA repair	X	X			Olaparib Talazoparib
✓ Few/rare alterations ✓ NTRK fusions (secretory) ✓ HER2 (lobular) ✓ dMMR/MSI-H	 X X X	 X X X			 Entrectinib Neratinib Pembrolizumab
TARGET - for anti-drug conjugates & delivery of toxic payloads					
✓ HER2	X	X	X	Trastuzumab deruxtecan	
✓ TROP2	X	X	X	Sacitizumab govitecan	

Biomarkers for Systemic Therapy in Metastatic Breast Cancer: ASCO Guideline Update

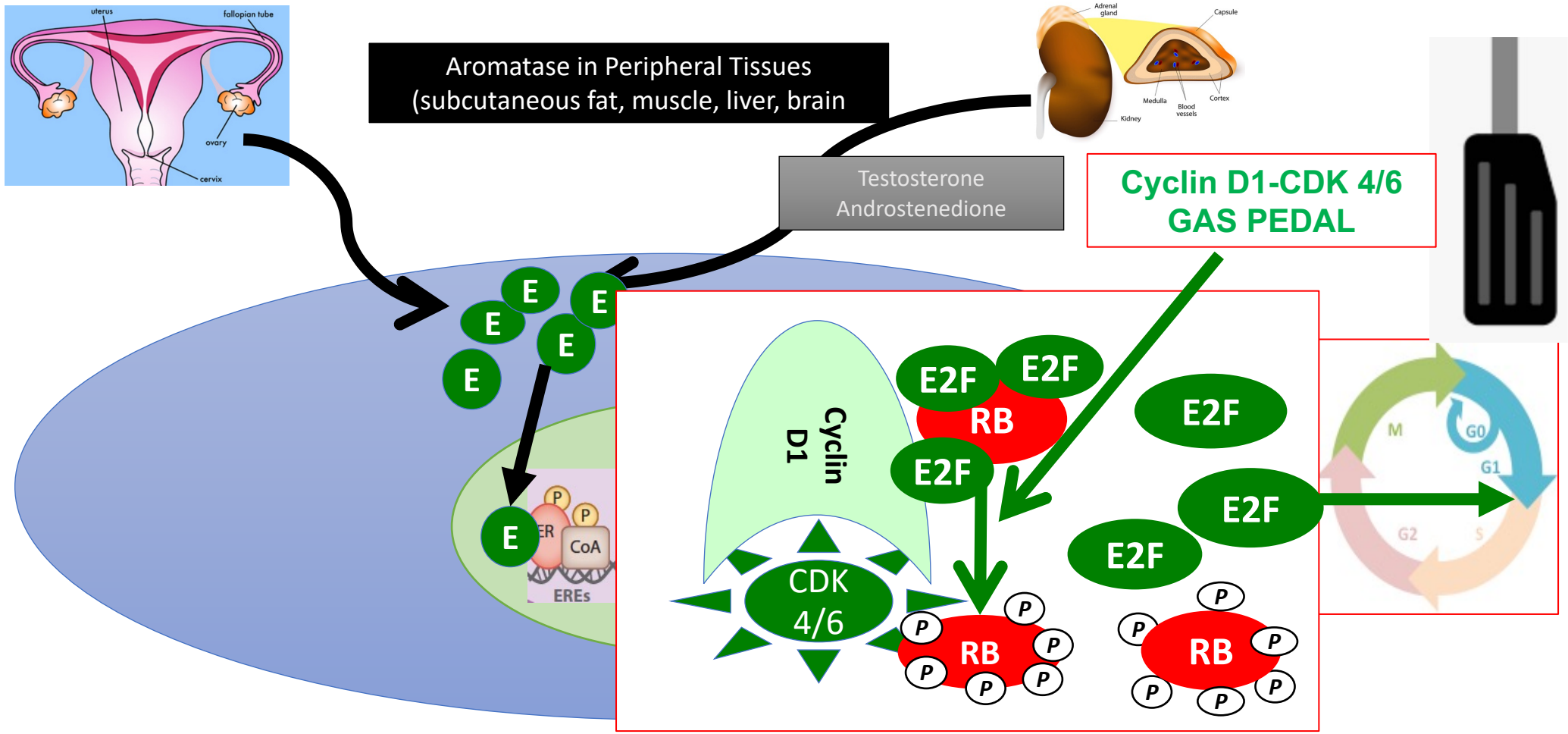
Test	Type of Recommendation	Quality of Evidence	Strength of Recommendation
Biomarker tests recommended by the ASCO expert panel			
PIK3CA	Evidence-based	High	Strong
Germline *BRCA1* and *BRCA2*	Evidence-based	High	Strong
PD-L1	Evidence-based	Intermediate	Strong
dMMR/MSI-H	Informal consensus-based	Low	Moderate
TMB	Informal consensus-based	Low	Moderate
NTRK fusions	Informal consensus-based	Low	Moderate
Biomarker tests not recommended by the ASCO expert panel			
ESR1	Evidence-based	Insufficient	Moderate
PALB2	Evidence-based	Low	Moderate
HRD	Informal consensus-based	Low	Moderate
TROP2 expression	Informal consensus-based	Low	Moderate
ctDNA	Informal consensus-based	Low	Moderate
CTCs	Informal consensus-based	Low	Moderate

Henry et al. J Clin Oncol 2022 (PMID: 35759724)

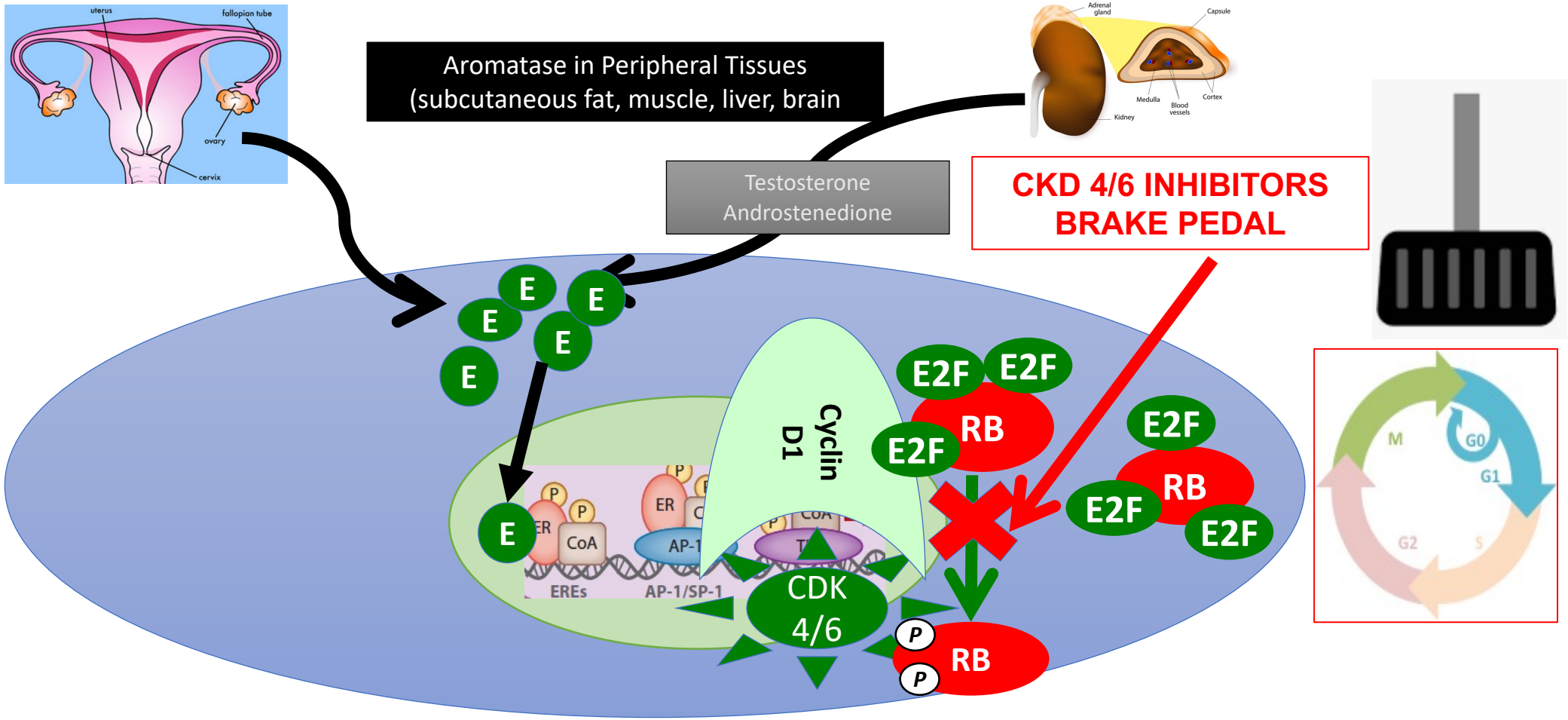
Antiestrogen Therapy and CDK 4/6 Inhibitors



Antiestrogen Therapy and CDK 4/6 Inhibitors



Antiestrogen Therapy and CDK 4/6 Inhibitors

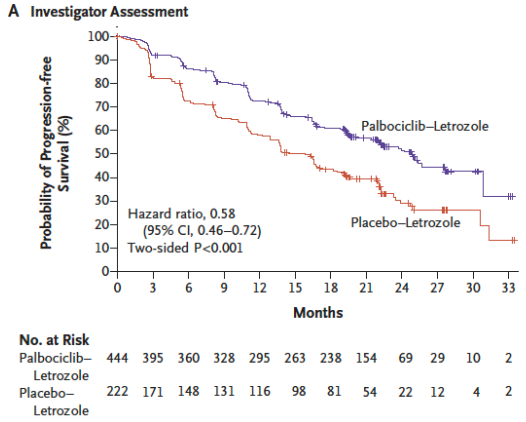
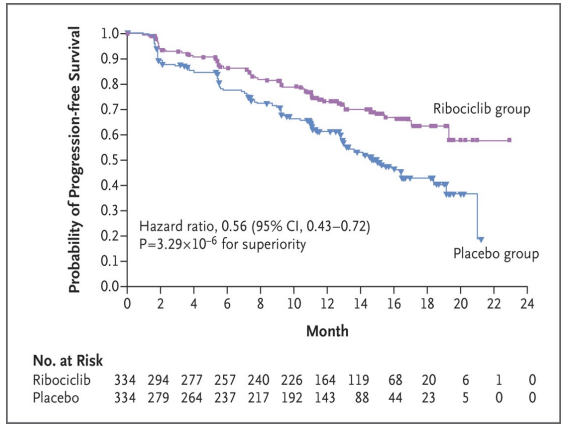
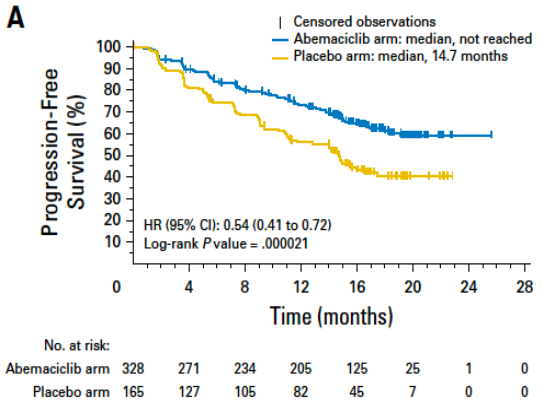


Summary of Characteristics and Adverse Effects of CDK4/6 Inhibitors

	Palbociclib	Ribociclib	Abemaciclib
IC50 In Vitro*	CDK4: 9-11 μM CDK6: 15 μM	CDK4: 11 μM CDK6: 39 μM	CDK4: 2 μM CDK6: 5 μM
Dose/Schedule	125 mg QD x 21/28 days	600 mg QD x 21/28 days	150 mg BID continuous
Neutropenia	+++	+++	++
Nausea	+	++	+
Diarrhea	+	+	+++
Transaminase elevation	+	++	+
Creatinine elevation			+
QT prolongation		+	
Tamoxifen interaction	No	Yes	No
Dose modification Reduction Interruption Discontinuation	36% vs 1% 70% vs. 42% 10% vs. 6% (Paloma2)	54% vs. 7% 77% vs. 41% 8% vs. 2% (Monaleesa2)	43% vs. 6% 56% vs. 19% 20% vs. 3% (Monarch3)

*DeMichele A, et al. *Clin Cancer Res.* 2015 (PMID: 25501126)

A.I.s +/- CDK 4/6 Inhibitors as First-Line Endocrine Therapy in Postmenopausal Women (investigator assessment of response/progression)

	PALOMA 2 (Palbociclib)	MONALEESA2 (Ribociclib)	MONARCH3 (Abemaciclib)
Progression-Free Survival (PFS)			
Median PFS	24.8 vs.14.5 mo. HR 0.58, <0.001	25.3 vs. 16.0 mo. HR 0.56, p<0.000003	28.2 vs. 14.7 mo. HR 0.54 p=0.00002
Median OS	**Final Analysis:** Median FU 90 months 53.9 vs. 51.2 mo. HR=0.956 [95% CI, 0.777–1.177] P=0.3378	**Final Analysis:** Median FU 70 months OS 63.9 vs .51.4 mo. 0.76; (95% CI, 0.63 to 0.93) 2-sided P = 0.008	**Interim Analysis 2:** Median FU 64 months 67.1 vs. 54.5 mo. HR=0.75(95% CI: 0.58-0.97) p=0.0301 (threshold not met)
	Finn et al. NEJM 2016 (PMID: 27959613) Finn et al. ASCO 2022 (LBA1003)	Hortobagyi et al. NEJM 2015 (PMID: 27717303) Hortobagyi et al. NEJM 2022 (PMID: 35263519)	Goetz et al. J Clin Oncol 2017 (PMID: 28968163) Goetz et al. ESMO 2022 (LBA15)

Fulvestrant +/- CDK 4/6 Inhibitors as First or Second-Line Endocrine Therapy

PALOMA 3 (Palbociclib)

- Premenopausal: 21%
- PD after prior ET: 100%
- Prior chemo for mets: 34%

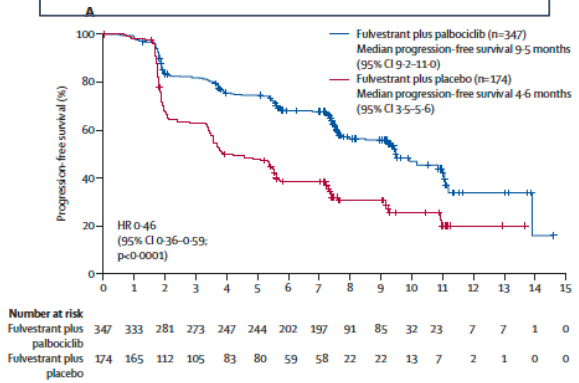
MONALEESA3 (Ribociclib)

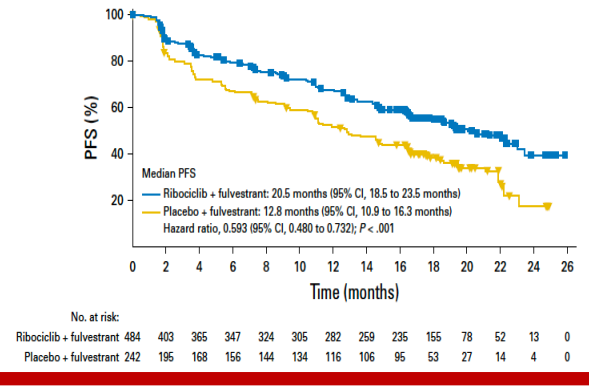
- Premenopausal: 0%
- PD after prior ET: 48%
- Prior chemo for mets: 0%

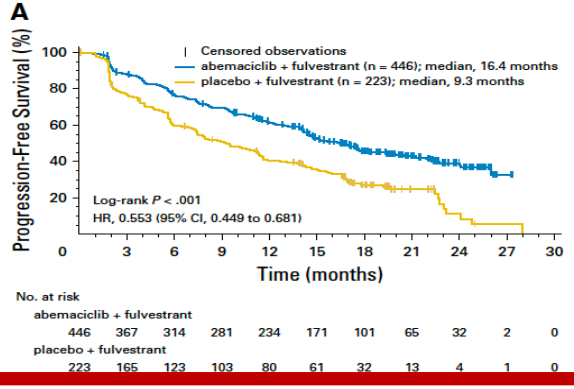
MONARCH2 (Abemaciclib)

- Premenopausal: 17%
- PD after prior ET:100%
- Prior chemo for mets: 38%

Progression-Free Survival (PFS)







Median PFS

PALOMA 3 (Palbociclib)	MONALEESA3 (Ribociclib)	MONARCH2 (Abemaciclib)
9.5 vs. 4.6 mo. HR 0.46, P<0.0001	Overall: 20.5 vs. 12.8 mo. HR 0.59, P<0.001 2nd Line 14.6 vs. 9.1 mo. HR 0.57 (95% CI 0.43-0.74)	16.4 vs. 9.3 mo. HR 0.55, P<0.001

Median OS

PALOMA 3 (Palbociclib)	MONALEESA3 (Ribociclib)	MONARCH2 (Abemaciclib)
Final Analysis Median FU 45 months 34.9 vs. 28.0 mo. **HR 0.81 (0.64-1.03), p=0.09** ET Sensitive (79%): 39.7 vs. 29.7 mo. **(HR 0.72, 95% CI 0.55, 0.94)**	**Updated Exploratory Analysis** Median FU 56 months 39.7 vs. 33.7 mo (2nd Line) HR 0.78 95% CI 0.59-1.04	**Interim Analysis 2** Median FU 48 months 46.7 vs. 37.3 mo. HR, 0.76 95% CI, 0.61-0.95; P = .01

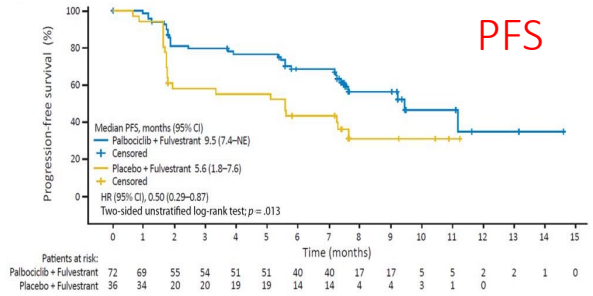
Cristofanilli et al. NEJM 2018 (PMID: 30345905)

Slamon et al. NEJM 2020 (PMID: 31826360)
Slamon et al Ann Oncol 2021 (PMID: 34102253)

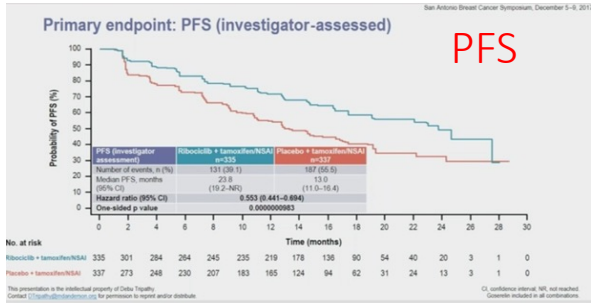
Sledge et al. JCO 2017 (PMID: 28580882)
Sledge et al. JAMA Oncol 2020 (PMID: 31563959)

Endocrine Therapy +/- CKD4/6 Inhibitors in Premenopausal Women Receiving OFS

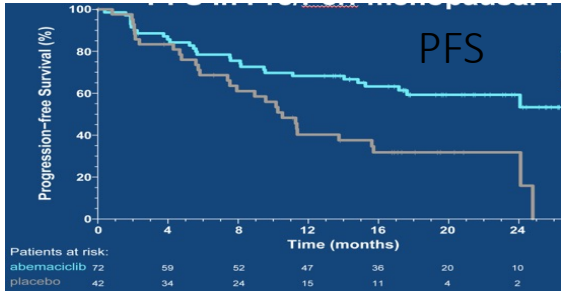
PALOMA-3 (N=106)
Fulvestrant + goserelin
HR 0.50, p=0.013

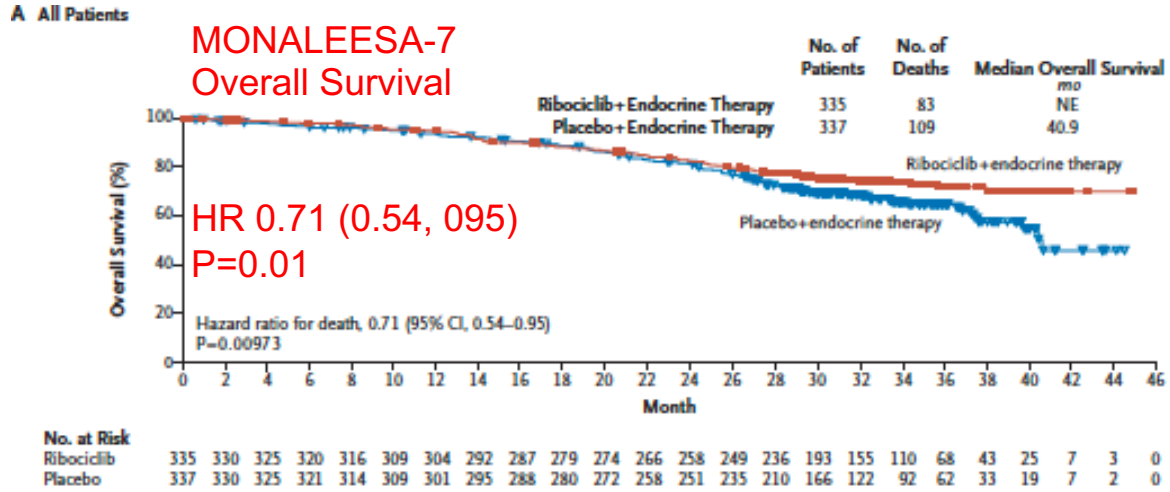


MONALEESA-7 (N=672)
Tamoxifen or NSAI + goserelin
HR 0.55, p<0.001



MONARCH-2 (N=114)
Fulvestrant + GnRH
HR 0.45, p=0.002





Loibl et al. Oncologist 2017 (PMID: 28652278); Neven et al. Breast Cancer Res 2021 (PMID: 34425869); Im et al. NEJM 2019 (PMID: 31166679)

monarchE Study Design (NCT03155997)

HR+, HER2-, node positive high-risk EBC
- Women or men
- Pre-/postmenopausal
- With or without prior neo- and/or adjuvant chemotherapy
- No metastatic disease
- Maximum of 16 months from surgery to randomization and 12 weeks of ET following the last non-ET

Cohort 1: High risk based on **clinical pathological features**
- ≥4 ALN OR
- 1-3 ALN and at least 1 of the below:
  - Grade 3 disease
  - Tumor size ≥5 cm

Cohort 2: High risk based on **Ki-67**
- 1-3 ALN and
- Ki-67 ≥20% and
- Grade 1-2 and tumor size <5 cm

Stratified for:
- Prior chemotherapy
- Menopausal status
- Region

R 1:1
N = 5637

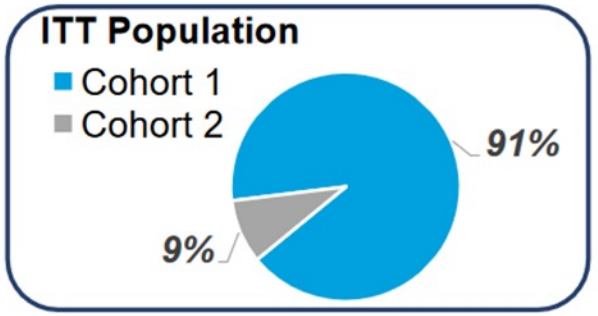
On-study treatment period
2 years

Abemaciclib
(150mg twice daily)
+
Endocrine Therapy: AI or tamoxifen

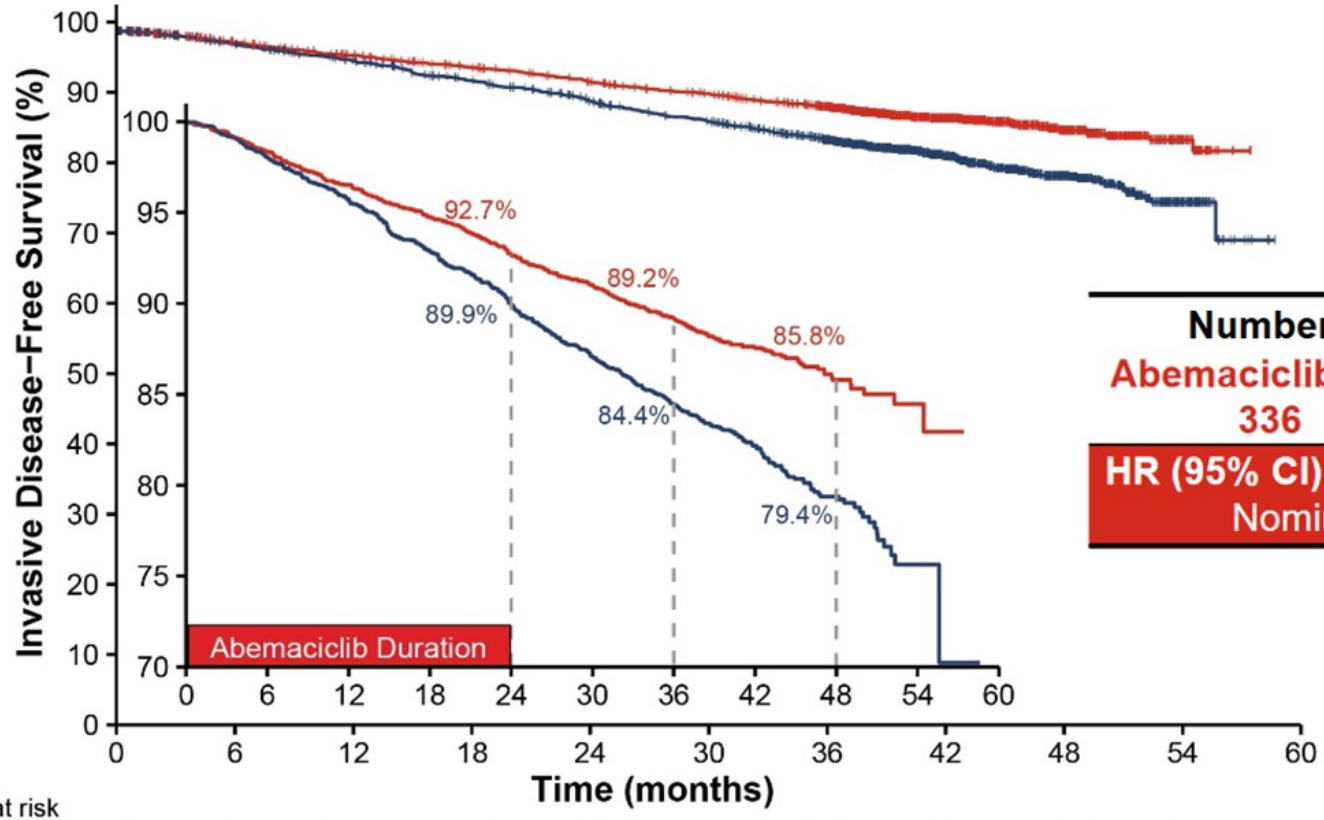
Endocrine Therapy: AI or tamoxifen

Follow-up period
Endocrine Therapy
3-8 years as clinically indicated

Primary Objective: IDFS
Secondary Objectives: IDFS in high Ki-67 populations, DRFS, OS, Safety, PK, PRO



IDFS Benefit in ITT Persists Beyond Completion of Abemaciclib



Number of IDFS events

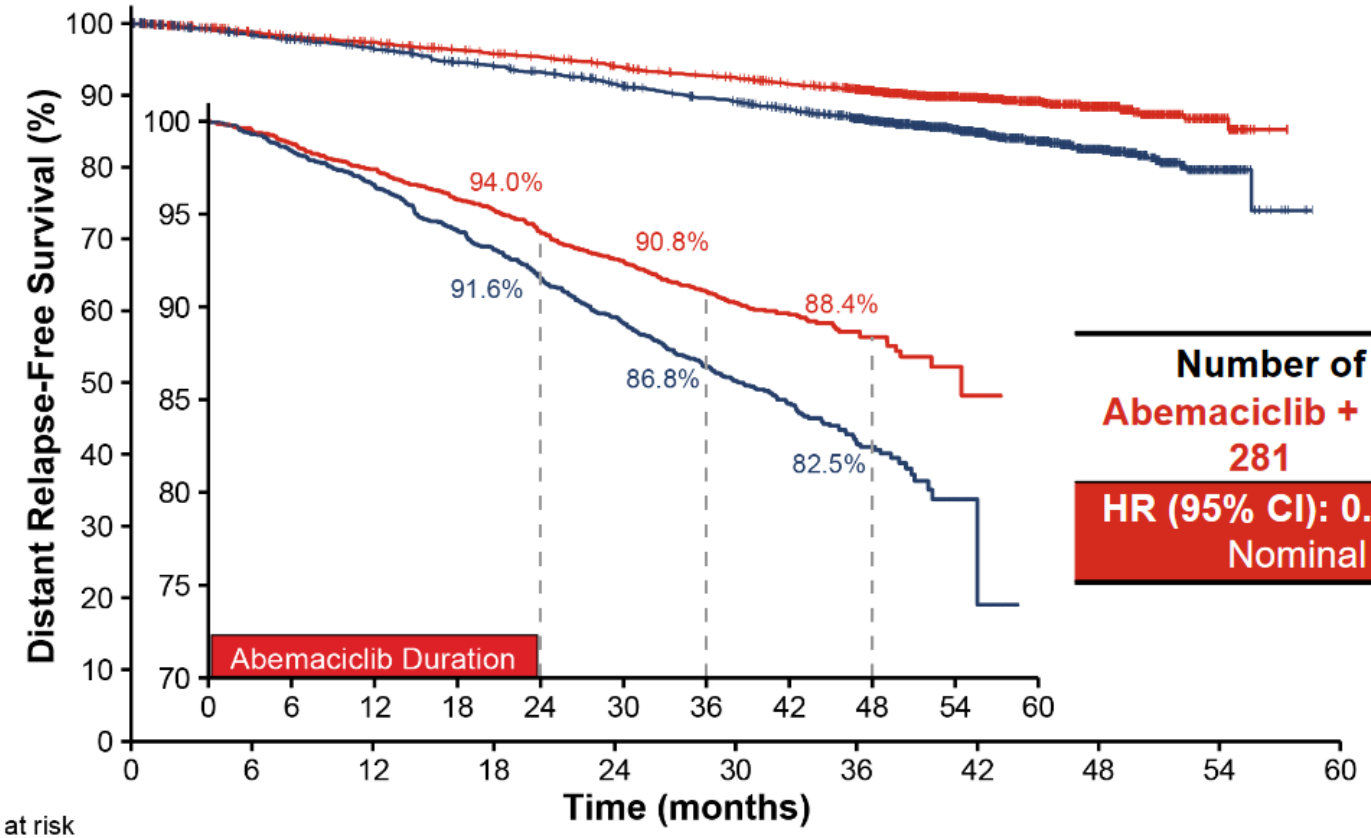
Abemaciclib + ET	ET Alone
336	499

HR (95% CI): 0.664 (0.578, 0.762)
Nominal p < 0.0001

33.6% reduction in the risk of developing an IDFS event with an increase in absolute benefit in IDFS 4-year rates (6.4%) compared to 2-and 3-year IDFS rates (2.8% and 4.8% respectively)

OFFICIAL best of 8 SABCS EAST PROGRAM

DRFS Benefit in ITT Persists Beyond Completion of Abemaciclib



Number at risk											
Abemaciclib + ET	2808	2629	2567	2500	2434	2374	2244	1251	535	81	0
ET Alone	2829	2659	2589	2499	2410	2327	2151	1231	526	85	0

Number of DRFS events

Abemaciclib + ET	ET Alone
281	421

HR (95% CI): 0.659 (0.567, 0.767)
Nominal p < 0.0001

34.1% reduction in the risk of developing a DRFS event with an increase in absolute benefit in DRFS 4-year rates (5.9%), compared to 2-and 3-year rates (2.5% and 4.1%, respectively)

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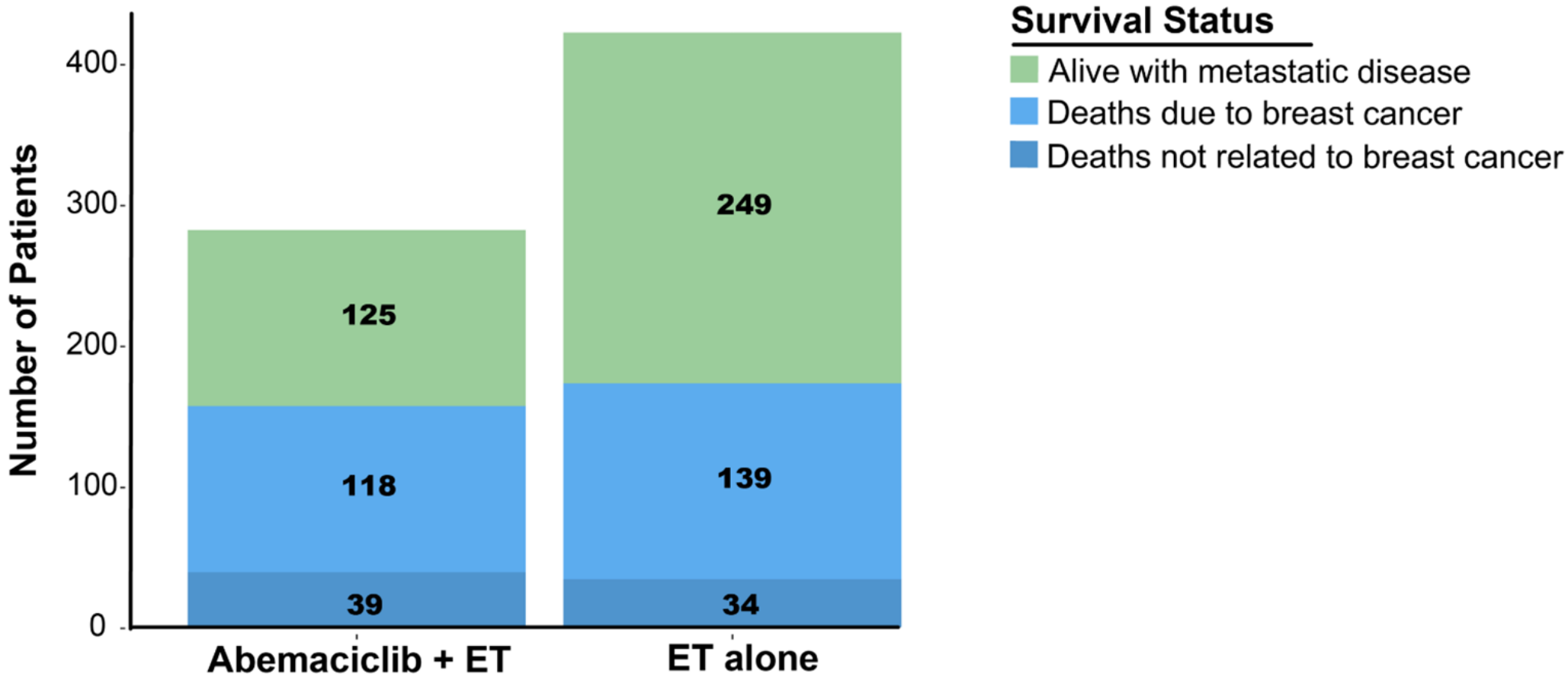
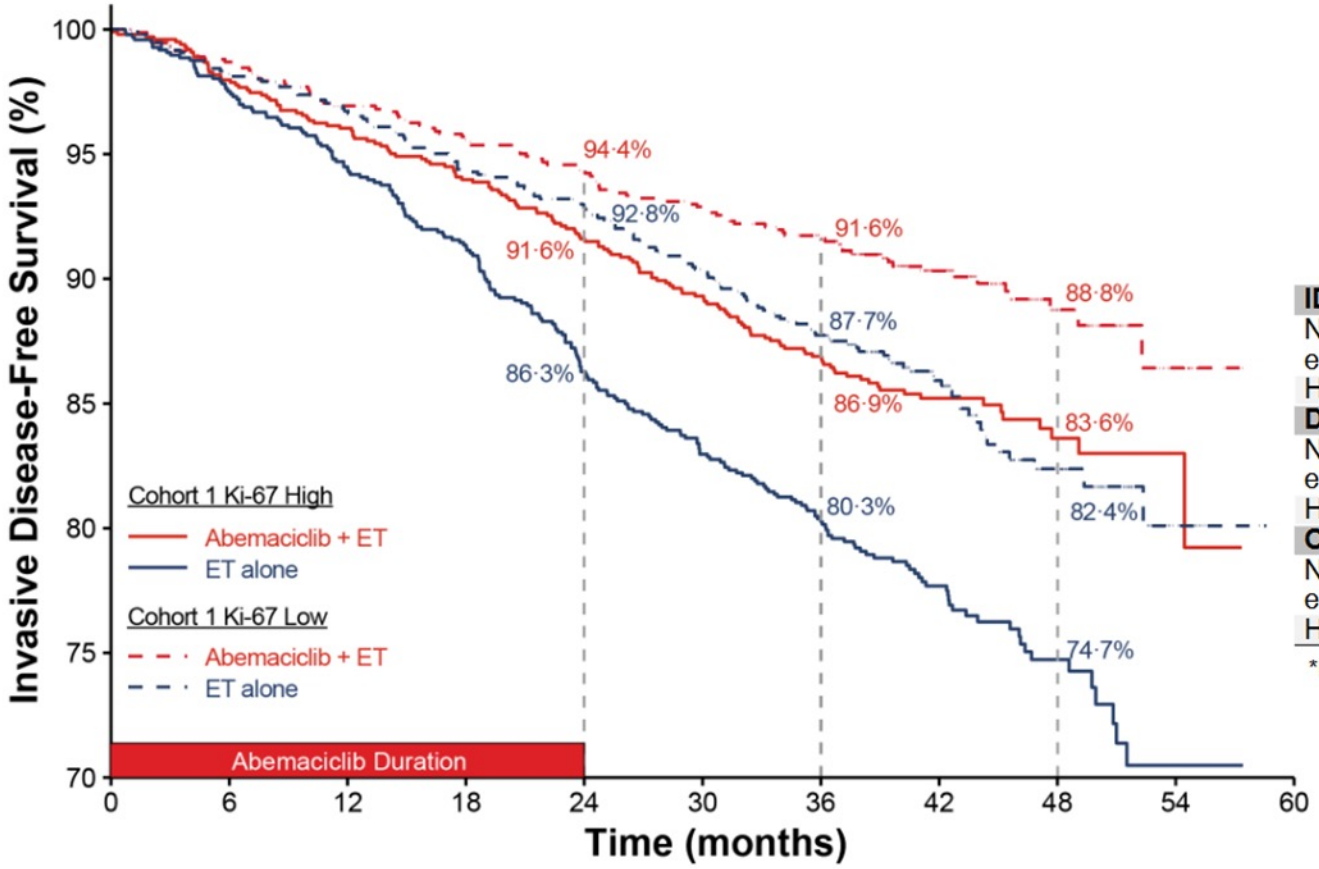
Fewer Patients with Metastatic Disease in the Abemaciclib arm



Ki-67 is Prognostic, but Not Predictive of Abemaciclib Benefit



	Cohort 1*			
	C1 Ki-67 High		C1 Ki-67 Low	
	Abemaciclib + ET N=1017	ET alone N=986	Abemaciclib + ET N=946	ET alone N=968
IDFS				
Number of events, n	147	224	91	141
HR (95% CI)	**0.618** (0.501, 0.762)		**0.624** (0.478, 0.814)	
DRFS				
Number of events, n	126	193	74	119
HR (95% CI)	**0.612** (0.488, 0.767)		**0.613** (0.458, 0.821)	
OS (Immature)				
Number of events, n	68	88	39	50
HR (95% CI)	**0.733** (0.533, 1.007)		**0.772** (0.506, 1.175)	

*Ki-67 value was missing in 1203 (23.5%) patients

Within Cohort 1, similar abemaciclib treatment effects were observed regardless of Ki-67 index

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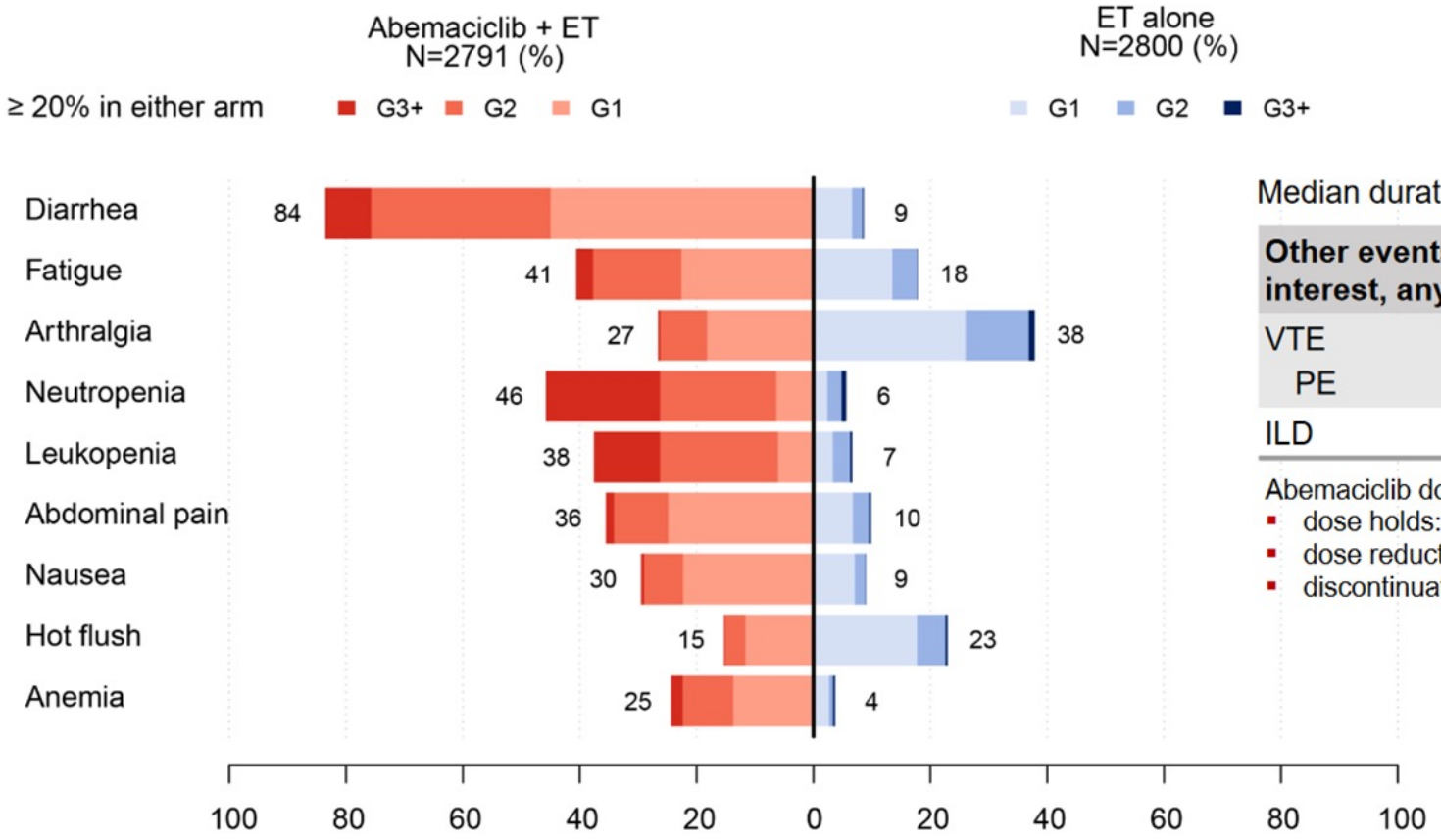
Safety Findings Consistent with Previous Analyses



Median duration of abemaciclib: 23.7 months.

Other events of interest, any grade	Abemaciclib + ET N = 2791, %	ET Alone N = 2800, %
VTE	2.5	0.7
PE	1.0	0.1
ILD	3.3	1.3

Abemaciclib dose adjustments due to AEs

- dose holds: 61.7%
- dose reductions: 43.6%
- discontinuations 18.5% [8.9% after dose reduction]

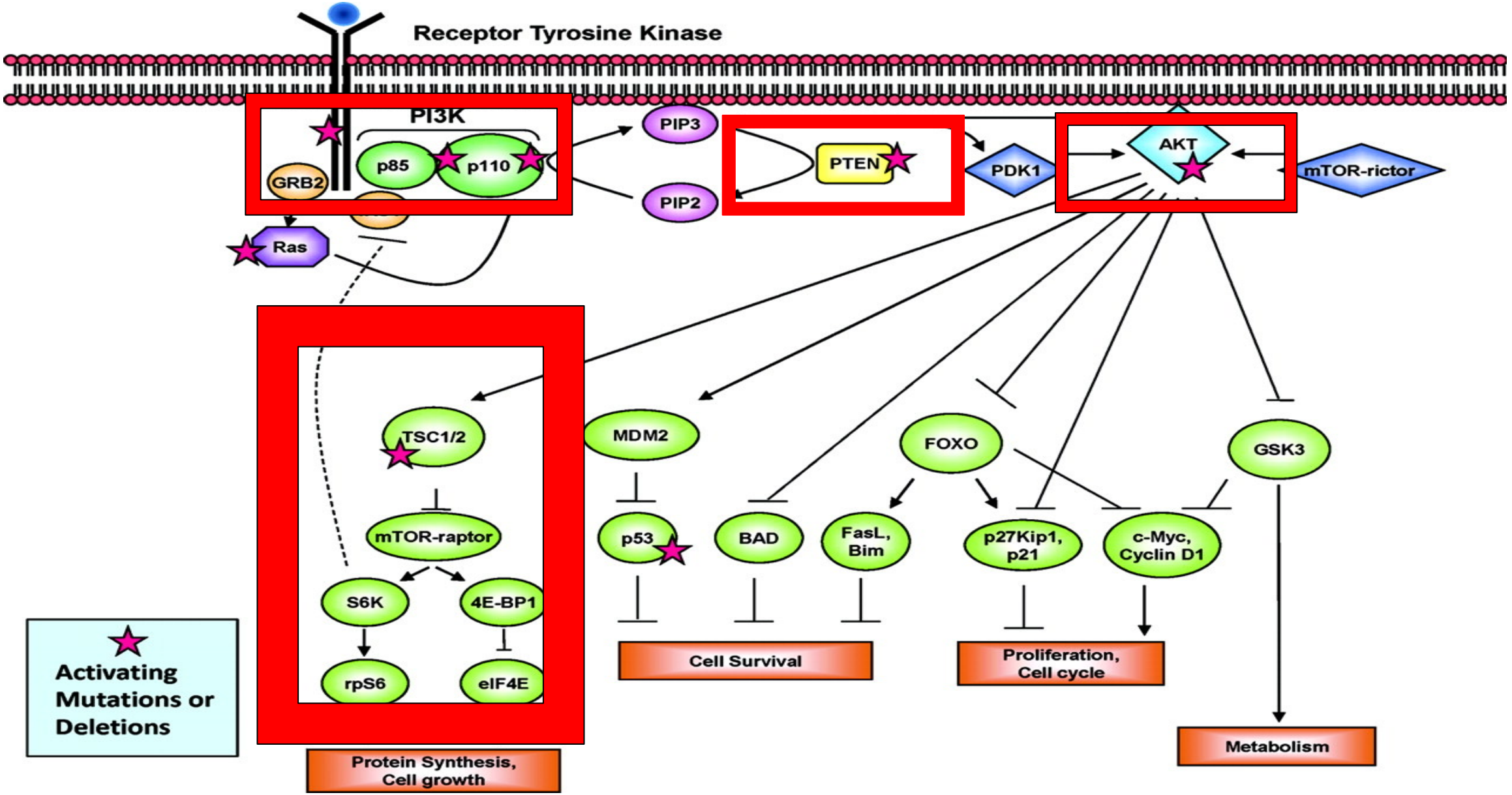
All patients who received at least one dose of study treatment were included in the safety population

The safety profile of abemaciclib is considered manageable and acceptable for this high-risk population

OFFICIAL best of 8 SABCS EAST PROGRAM

PI3K/AKT/M-TOR Pathway

Most commonly dysregulated pathway in breast cancer



Biomarkers for Systemic Therapy in Metastatic Breast Cancer: ASCO Guideline Update

Test	Type of Recommendation	Quality of Evidence	Strength of Recommendation
Biomarker tests recommended by the ASCO expert panel			
PIK3CA	Evidence-based	High	Strong
Germline *BRCA1* and *BRCA2*	Evidence-based	High	Strong
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ctDNA	Informal consensus-based	Low	Moderate
CTCs	Informal consensus-based	Low	Moderate

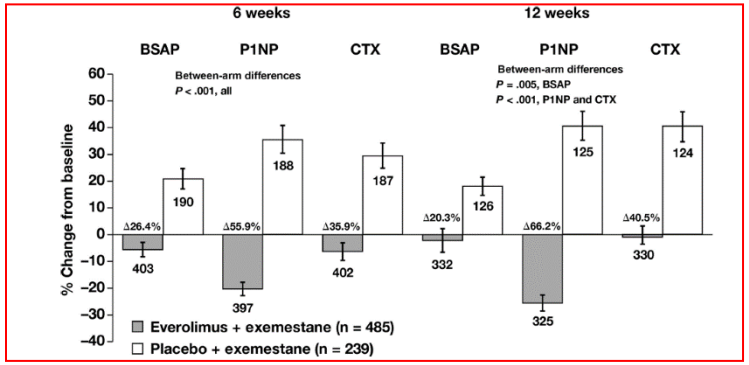
Henry et al. J Clin Oncol 2022 (PMID: 35759724)

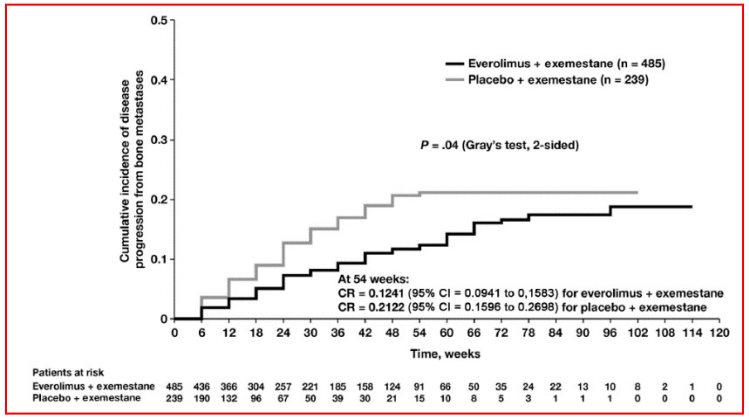
Randomized Trials of Endocrine Therapy +/- Everolimus in ER-Positive,HER2-Negative Metastatic Breast Cancer

Trial	Design	No.	Median PFS (mo.)	Median OS (mo.)
Bolero-2	Exemestane ± Eve/Placebo	724 Phase III	7.8 vs. 3.2 HR 0.45, p<0.0001	31.0 vs. 26.6 HR 0.89, p=0.1426
TAMRAD	Tamoxifen ± Everolimus	111 Phase II	8.6 vs. 4.5 HR 0.54 p=0.002	NR vs. 32.9 HR 0.45 p=0.007
PreCOG0102	Fulvestrant ± Eve/Placebo	131 Phase II	10.4 vs. 5.1 HR 0.6, p=0.02	28.3 vs. 31.4 HR 1.13, p=0.37
MANTA	Fulvestrant ± Eve/Placebo	130 Phase II	12.3 vs. 5.4 HR 0.61, p=0.02	Immature HR 0.56 p= 0.09

Baselga et al. NEJM 2012 (PMID: 22149876);Bachelot et al. J Clin Oncol 2012 (PMID: 22565002) Piccart et al. Ann Onc 2014 (PMID: 25231953); Kornblum et al. J Clin Oncol 2018 (PMID: 29664714); Schmid et al. JAMA Oncol 2019 (PMID: 31465093)

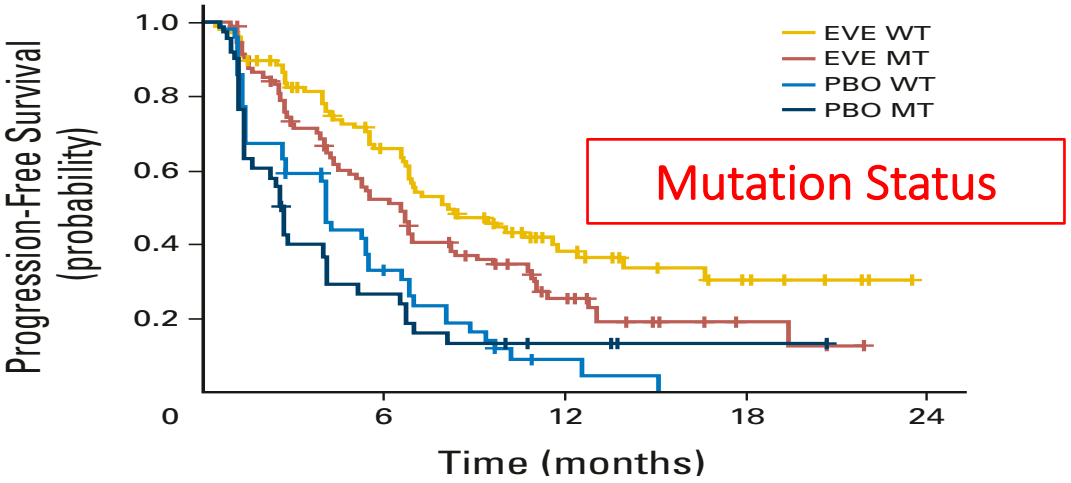
Effect of Everolimus on Bone Marker Levels and Progressive Disease in Bone in BOLERO-2



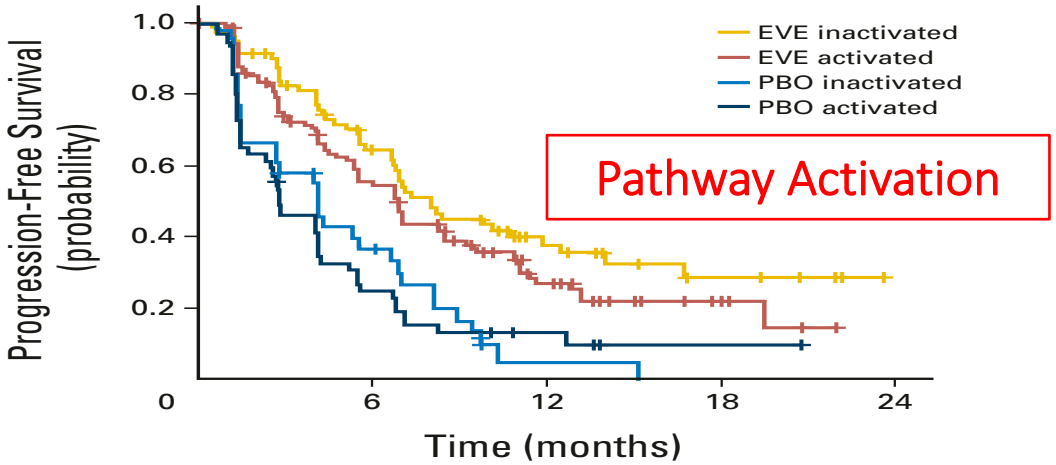


Gnant et al. JNCI 2013 (PMID: 23425564)

Everolimus: PIK3CA Mutation or Pathway Activation Status Not Predictive of Everolimus Benefit in BOLERO2

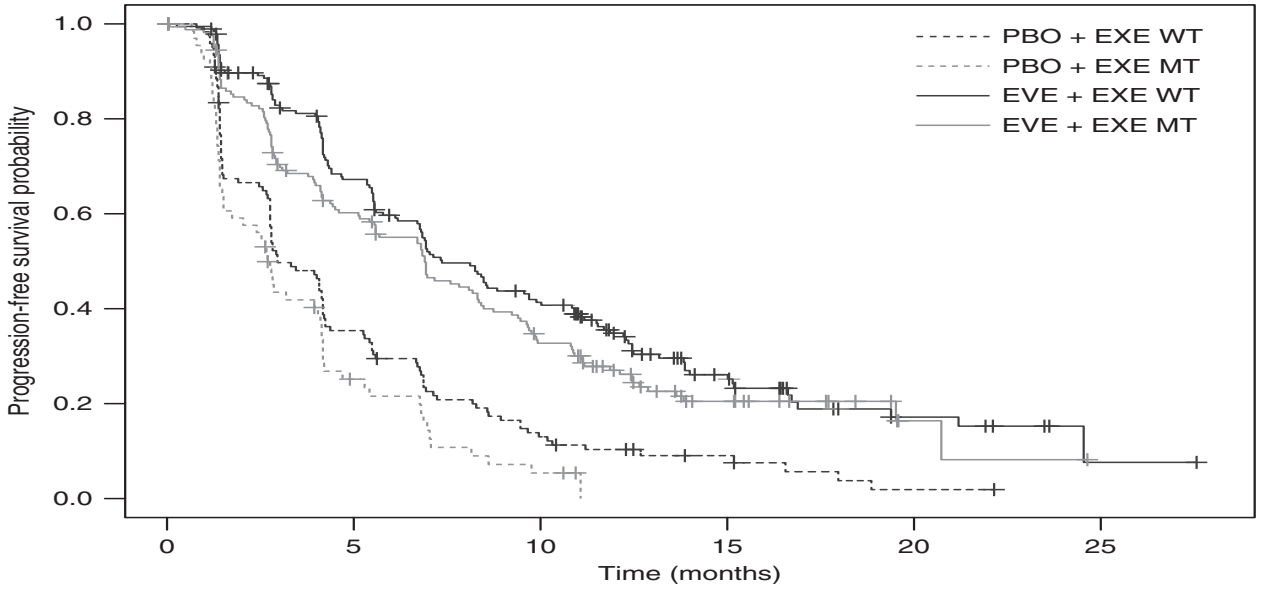


Mutation Status



Pathway Activation

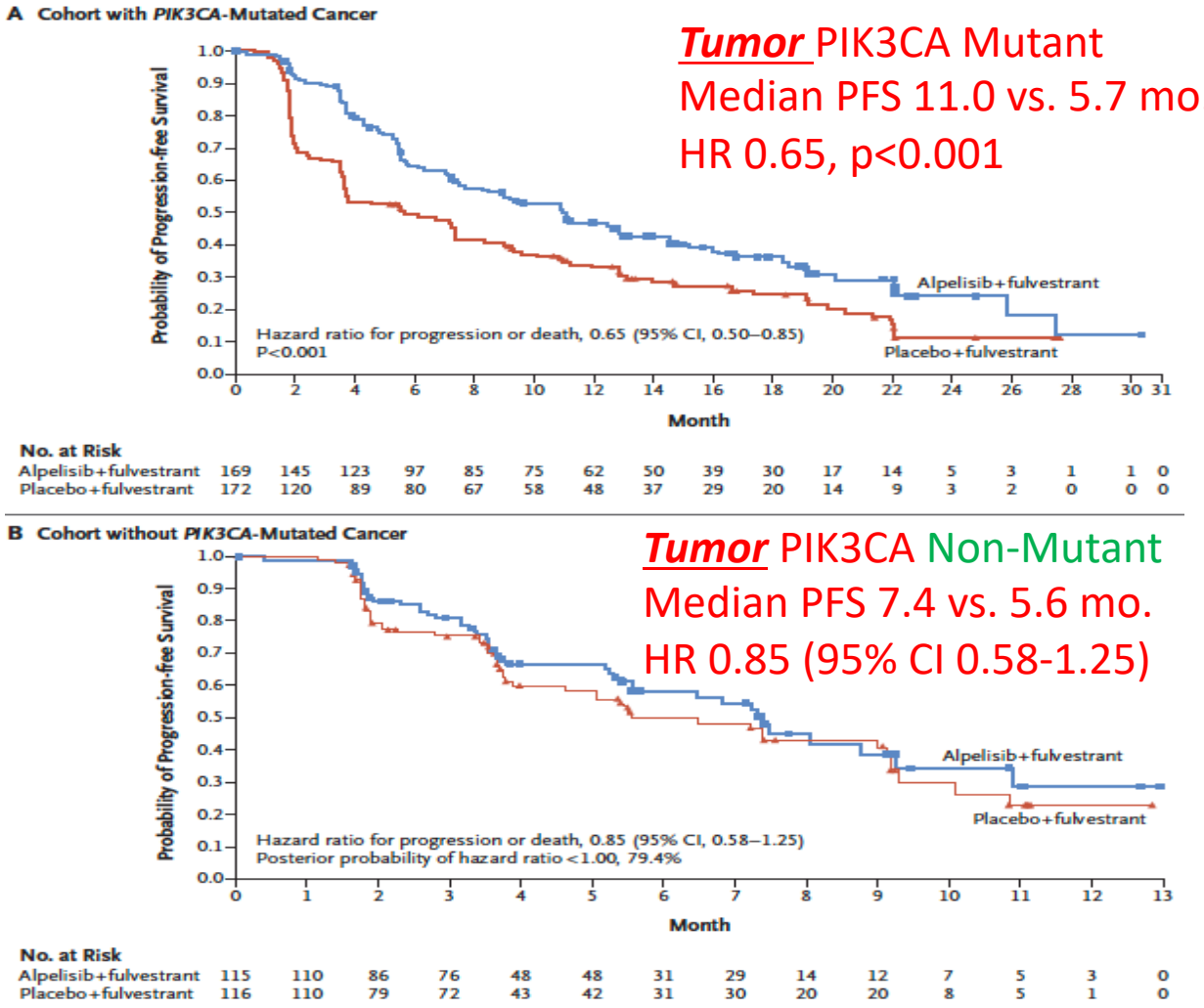
Tumor



ctDNA

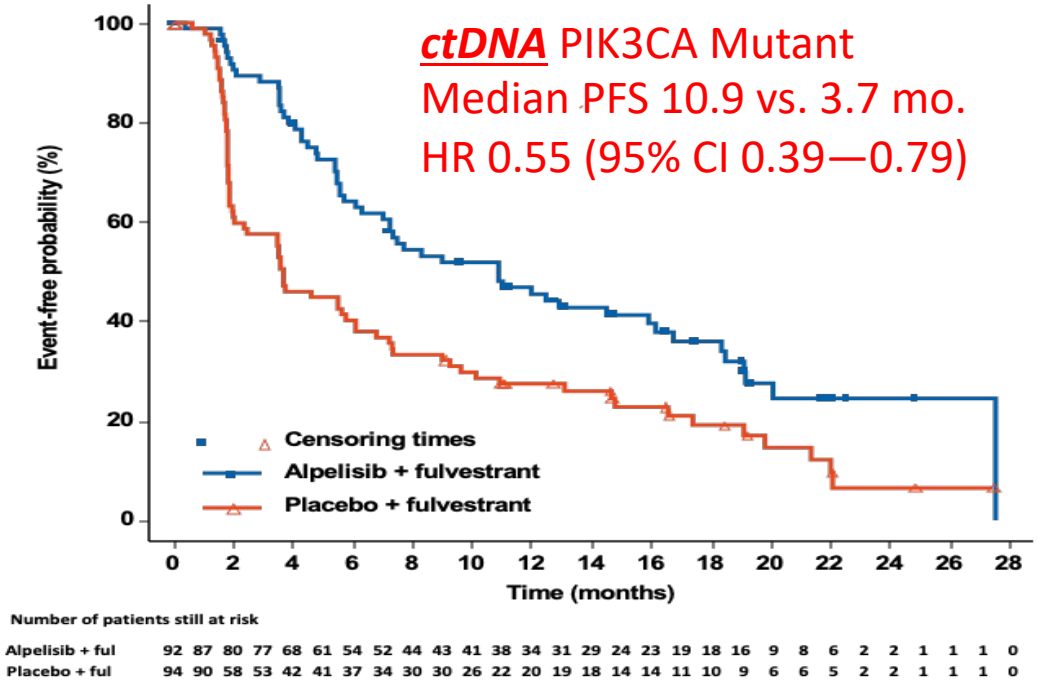
Hortobagyi et al. J Clin Oncol 2016 (PMID: 26503204)
Moynahan et al. Br J Cancer 2016 (PMID: 28183140)

SOLAR1: Efficacy of Alpelisib by Tumor & ctDNA PIK3CA Mutation Status: Progression-Free Survival (PFS)



Tumor PIK3CA Mutant
Median PFS 11.0 vs. 5.7 mo.
HR 0.65, p<0.001

Tumor PIK3CA Non-Mutant
Median PFS 7.4 vs. 5.6 mo.
HR 0.85 (95% CI 0.58-1.25)



ctDNA PIK3CA Mutant
Median PFS 10.9 vs. 3.7 mo.
HR 0.55 (95% CI 0.39—0.79)

	ALP + FUL		PBO + FUL		
	Event n/N (%)	Median PFS	Event n/N (%)	Median PFS	HR
Patients with PIK3CA mutation: tissue	103/169 (60.9)	11.0	129/172 (75.0)	5.7	0.65
Patients with PIK3CA mutation: plasma	57/92 (62.0)	10.9	75/94 (79.8)	3.7	0.55
Patients without PIK3CA mutation: tissue	49/115 (42.6)	7.4	57/116 (49.1)	5.6	0.85
Patients without PIK3CA mutation: plasma	92/181 (50.8)	8.8	103/182 (56.6)	7.3	0.80

Andre et al. NEJM 2019 (PMID: 31091374)
Juric et al. SABCS 2018 (GS3-08)

Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: Results from the Phase III CAPItello-291 trial

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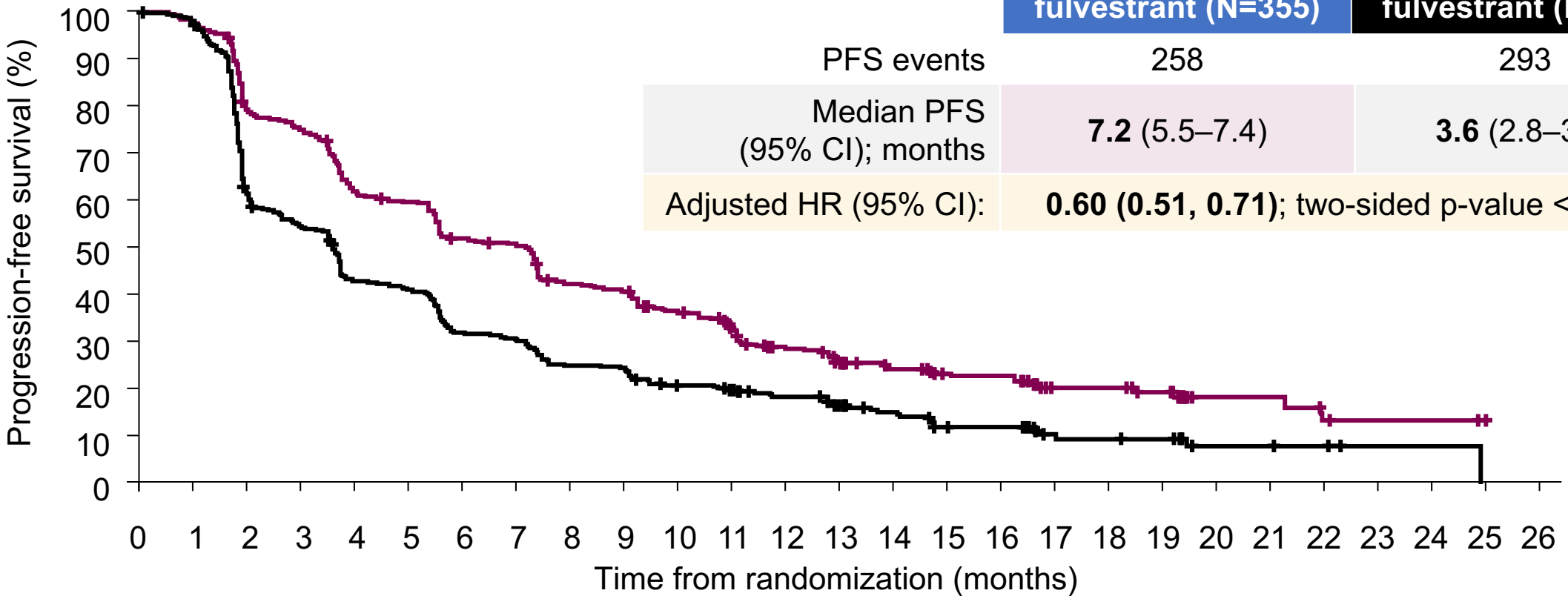
Dual-primary endpoint: Investigator-assessed PFS in the overall population

	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
PFS events	258	293
Median PFS (95% CI); months	**7.2** (5.5–7.4)	**3.6** (2.8–3.7)
Adjusted HR (95% CI):	**0.60 (0.51, 0.71)**; two-sided p-value <0.001	



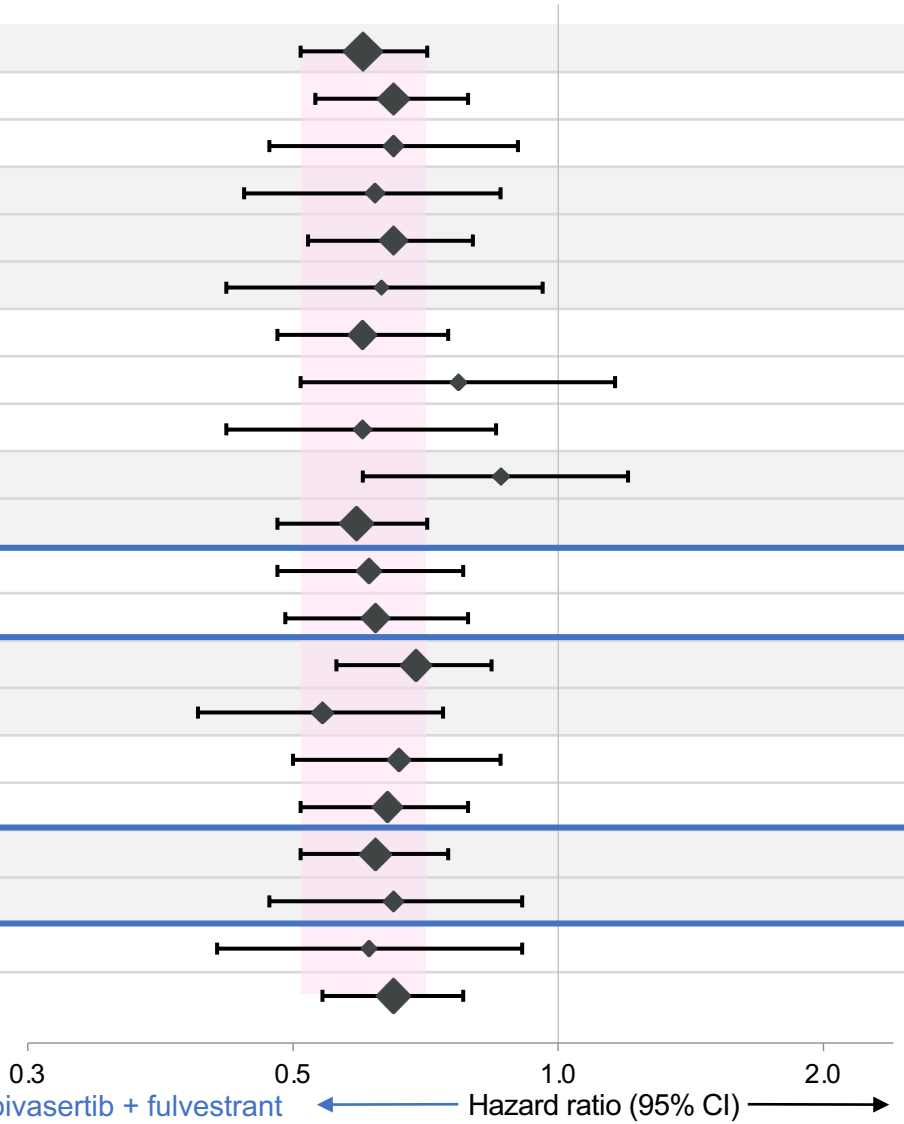
Number of patients at risk

Capivasertib + fulvestrant	355	330	266	252	207	199	172	166	138	133	115	98	78	64	55	44	43	25	25	21	8	8	5	2	2	1	0
Placebo + fulvestrant	353	329	207	182	142	136	106	100	83	81	66	59	51	41	33	24	23	12	11	10	4	4	3	1	1	0	0

+ indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases, prior use of CDK4/6 inhibitor, and geographic region.

Investigator-assessed PFS by subgroup: Overall population

		Number of patients	HR (95%CI)
All patients		**708**	**0.60 (0.51, 0.71)**
Age	<65 years	491	0.65 (0.53, 0.79)
	≥65 years	217	0.65 (0.47, 0.90)
Race	Asian	189	0.62 (0.44, 0.86)
	White	407	0.65 (0.52, 0.80)
	Other	112	0.63 (0.42, 0.96)
Region	1	395	0.60 (0.48, 0.75)
	2	136	0.77 (0.51, 1.16)
	3	177	0.60 (0.42, 0.85)
Menopausal status (females only)	Pre/peri	154	0.86 (0.60, 1.20)
	Post	547	0.59 (0.48, 0.71)
Liver metastases	Yes	306	0.61 (0.48, 0.78)
	No	402	0.62 (0.49, 0.79)
Visceral metastases	Yes	478	0.69 (0.56, 0.84)
	No	230	0.54 (0.39, 0.74)
Endocrine resistance	Primary	262	0.66 (0.50, 0.86)
	Secondary	446	0.64 (0.51, 0.79)
Prior use of CDK4/6 inhibitors	Yes	496	0.62 (0.51, 0.75)
	No	212	0.65 (0.47, 0.91)
Prior chemotherapy for ABC	Yes	129	0.61 (0.41, 0.91)
	No	579	0.65 (0.54, 0.78)



Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia; Region 3: Asia. Primary and secondary resistance as per ESMO definition.

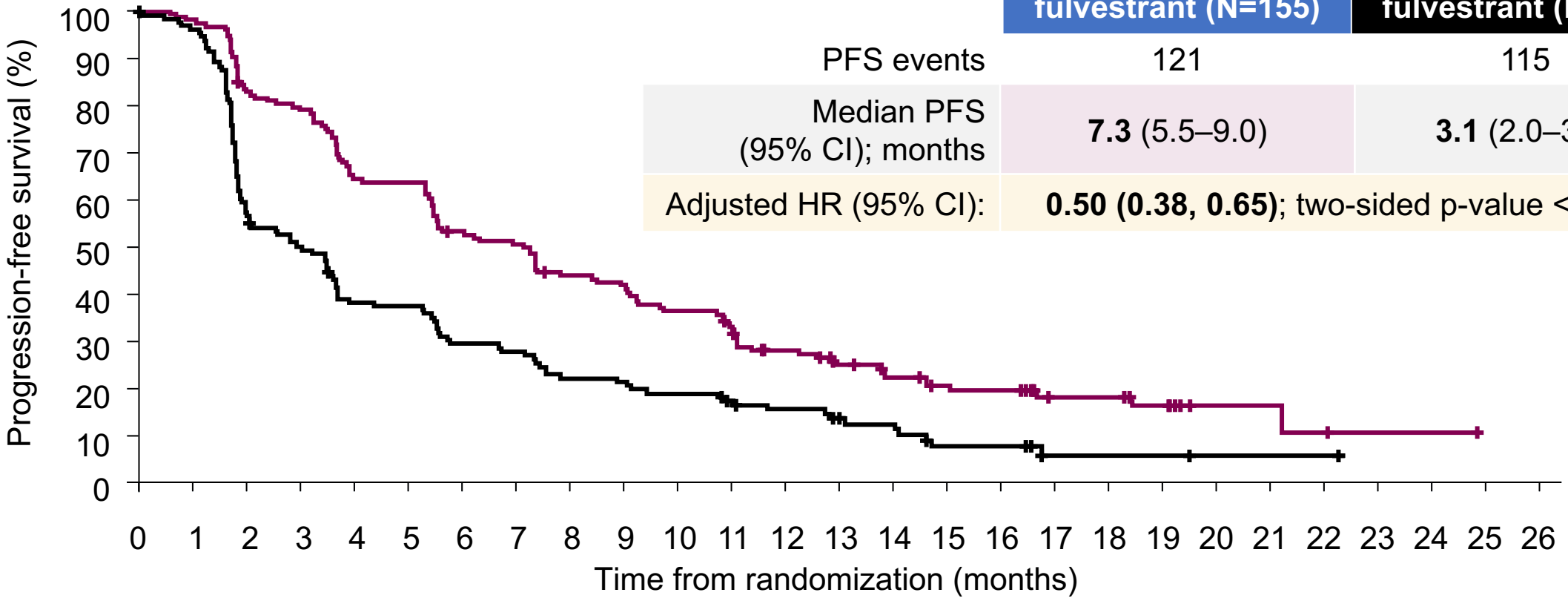
AKT pathway alterations

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

Dual-primary endpoint: Investigator-assessed PFS in the AKT pathway-altered population

	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
PFS events	121	115
Median PFS (95% CI); months	**7.3** (5.5–9.0)	**3.1** (2.0–3.7)
Adjusted HR (95% CI):	**0.50 (0.38, 0.65)**; two-sided p-value <0.001	

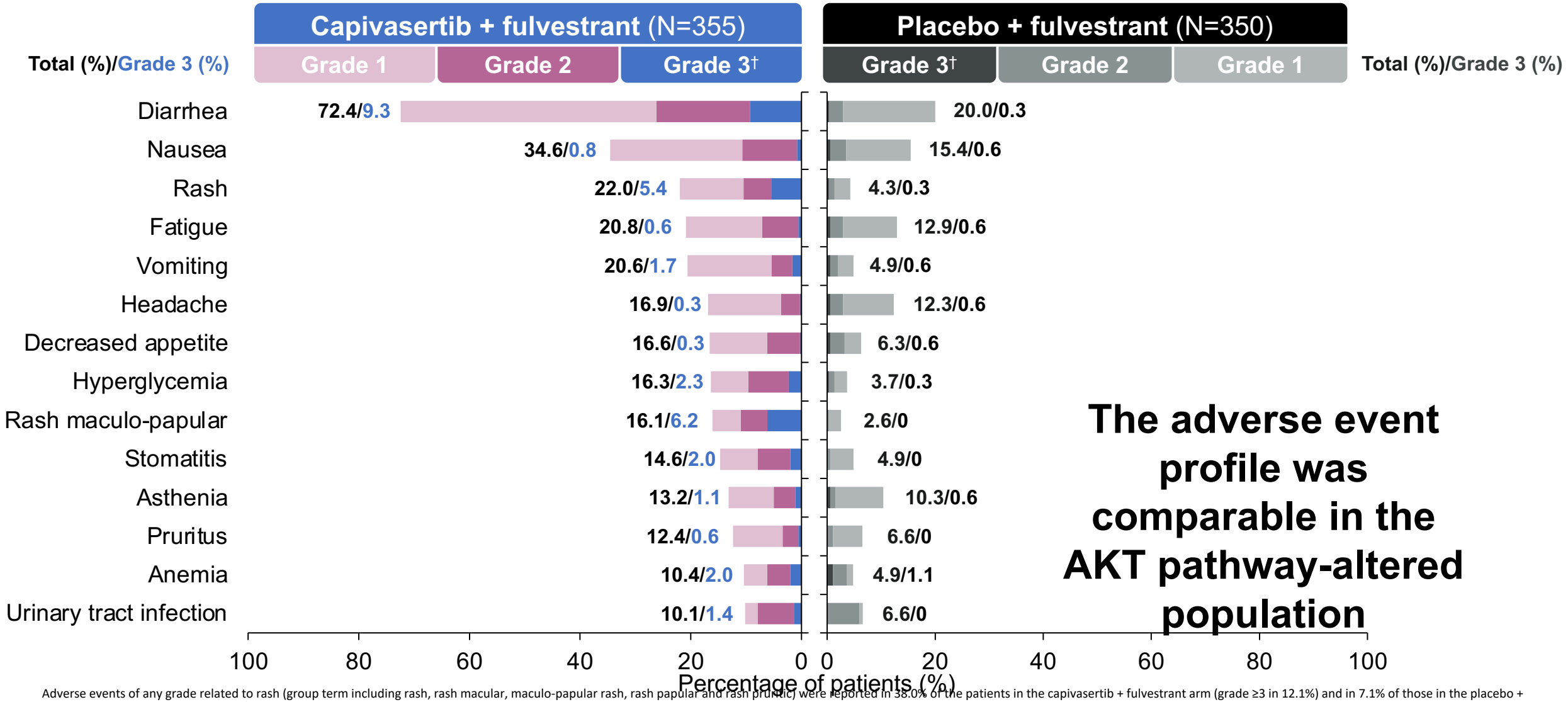


Number of patients at risk

Capivasertib + fulvestrant	155	150	127	121	99	97	80	76	65	62	54	49	38	31	26	22	21	12	12	9	3	3	2	1	1	0	0
Placebo + fulvestrant	134	124	77	64	48	47	37	35	28	27	24	20	17	14	11	6	6	2	2	2	1	1	1	0	0	0	0

+ indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and prior use of CDK4/6 inhibitor.

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



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

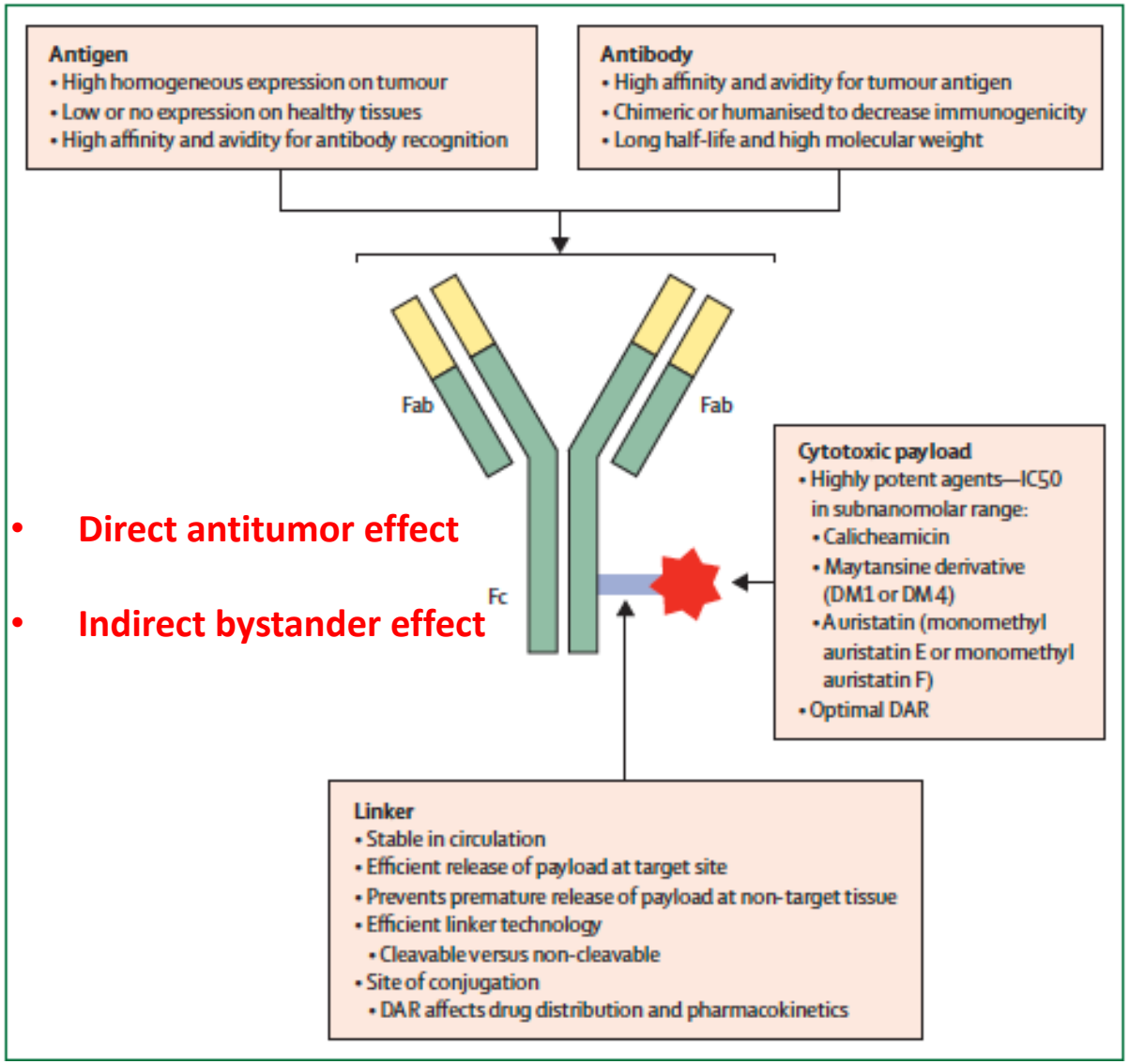
Adverse events of any grade related to rash (group term including rash, rash macular, maculo-papular rash, rash papular and rash pruritic) were reported in 38.0% of the patients in the capivasertib + fulvestrant arm (grade ≥3 in 12.1%) and in 7.1% of those in the placebo + fulvestrant group (grade ≥3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

Pathway Directed Oral Targeted Agents for ER-Positive, HER2-Negative Metastatic Breast Cancer

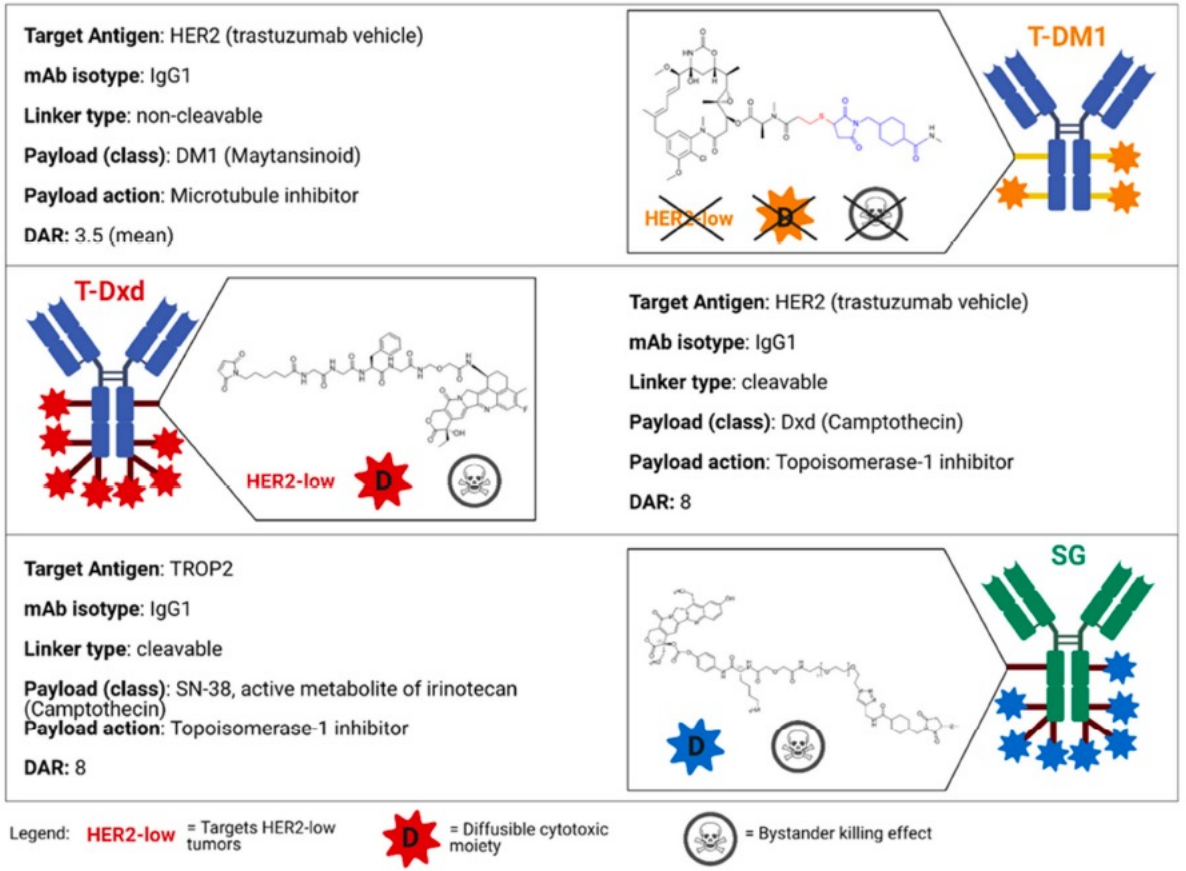
	Palbociclib	Ribociclib	Abemaciclib	Alpelisib	Everolimus
Class	CDK4/6 inhibitor	CDK4/6 inhibitor	CDK4/6 inhibitor	PIK3CA inhibitor	mTOR inhibitor
Dose	125 mg PO QD D1-21/28	600 mg QD D1-21/28	150 mg BID continuous	300 mg QD Continuous	10 mg QD Continuous
CYP3A4 Substrate	Major	Major	Major	Minor	Major
Setting	1st Line 2nd Line	1st Line 2nd Line	1s Line 2nd Line	2nd Line	2nd Line
Endocrine Rx	AI or fulvestrant	AI or fulvestrant	AI or fulvestrant	Fulvestrant	Exemestane or fulvestrant
PFS	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
OS	No – Overall **Yes-ET Sensitive**	**Yes**	**Yes**	No	No
Dose reduce (or stopped)	36 (10%) Paloma2	54% (8%) Monalessa2	43% (20%) Monarch3	64% (25%) Solar1	?? (19%) Bolero2
Most common toxicity	Neutropenia	Neutropenia	Diarrhea	DM, Rash, Diarrhea	Stomatitis, Rash
Cost (28 days)*	$14,939	$15,891	$14,852	$19,622	$18,846

Potent CYP3A4 inhibitors: clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, ritonavir, verapamil, goldenseal and grapefruit.
Potent CYP3A4 inducers: phenobarbital, phenytoin, rifampicin, St. John's Wort and glucocorticoids.
*Up-to-Date – accessed 11/1/20 (based on 28-day course of therapy)

Target Directed Therapy - Antibody Drug Conjugates



- **Direct antitumor effect**
- **Indirect bystander effect**



Chau et al. Lancet 2019 (PMID: 31478503)
Corti et al. Cancers 2021 (PMID: 34207890)

Destiny Breast-04: TDXd vs. TPC as Second–Line Therapy for HER2-Low (1-2+ IHC, FISH-Neg) MBC

- An open-label, multicenter study (NCT03734029)

- HER2-low (IHC 1+ vs IHC 2+/ISH-), unresectable, and/or MBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory[a]

Stratification
- Centrally assessed HER2 status[b] (IHC 1+ vs IHC 2+/ISH-)
- 1 vs 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) vs HR-

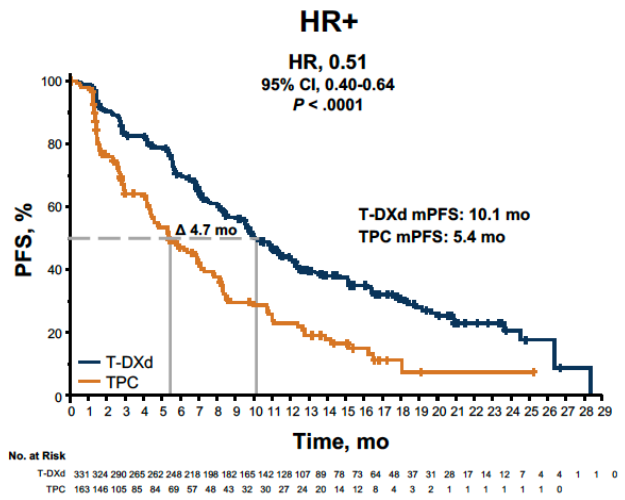
R 2:1

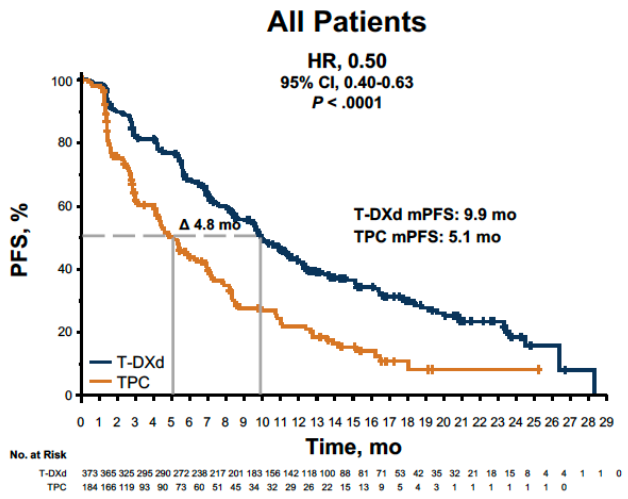
T-DXd
5.4 mg/kg Q3W
(n = 373)

HR+ ≈ 480
HR− ≈ 60

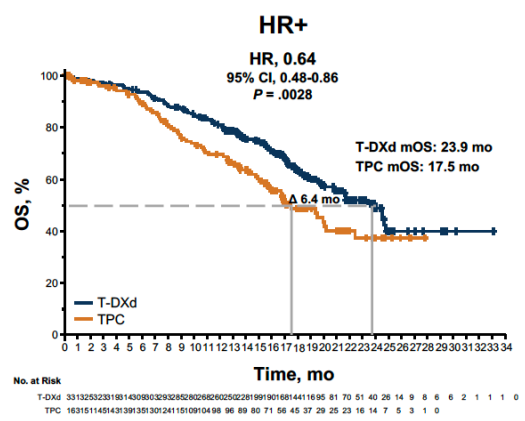
TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c] (n = 184)

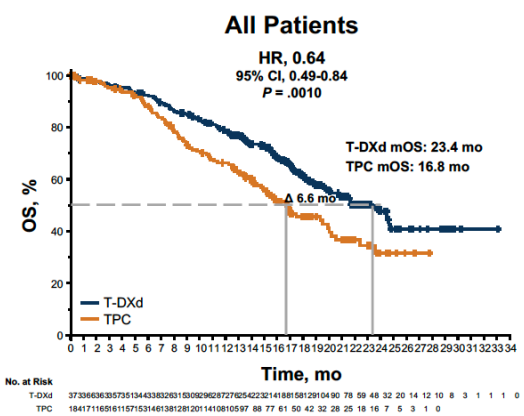
Primary Endpoint (BICR)
PFS in HR+ and All Patients[1,2]





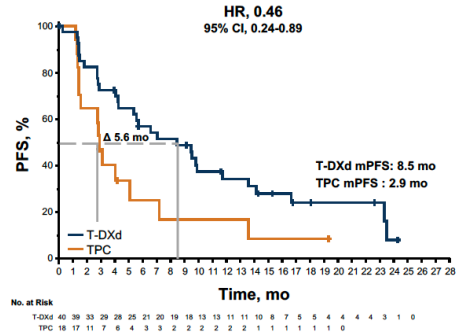
Secondary Endpoint
OS in HR+ and All Patients[1,2]

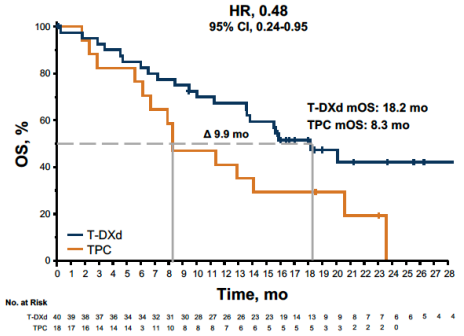




Exploratory Analyses
PFS and OS in HR- (Exploratory Endpoints)[1,2]

Hormone Receptor Negative





1. Modi et al. N Eng J Med 2022 (PMID: 35665782)
2. Modi et al. ASCO 2022 Plenary Session, LBA1

TROPICS-02: Phase III Trial Sacituzumab Govitecan vs. TPC in ER+ MBC

Metastatic or locally recurrent inoperable HR+/HER2- breast cancer that progressed after[a]:

- At least 1 endocrine therapy, taxane, and CDK4/6i in any setting
- At least 2, but no more than 4, lines of chemotherapy for metastatic disease
- Measurable disease by RECIST 1.1

N=543[b]

R 1:1

Treatment was continued until progression or unacceptable toxicity

Sacituzumab govitecan
10 mg/kg IV
days 1 and 8, every 21 days
n=272

Treatment of physician's choice[c]
(capecitabine, vinorelbine, gemcitabine or eribulin)
n=271

Endpoints

Primary
- PFS by BICR

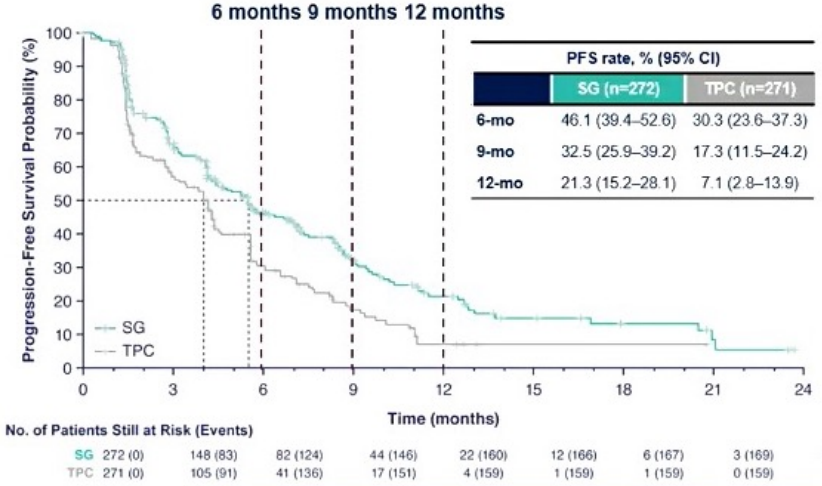
Secondary
- OS
- ORR, DOR, CBR by LIR and BICR
- PRO
- Safety

Stratification
- Visceral metastases (yes/no)
- Endocrine therapy in metastatic setting ≥6 months (yes/no)
- Prior lines of chemotherapies (2 vs 3/4)

PFS & OS in the ITT Population

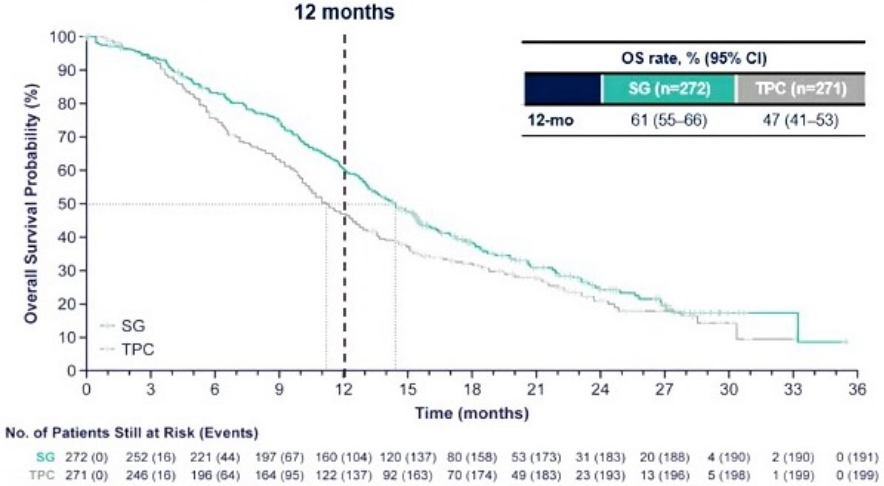
PFS[1]

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	0.0003	



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	



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

Rugo et al. ESMO 2022 (LBA76)

Antibody Drug Conjugates for Metastatic Breast Cancer

	Trastuzumab deruxtecan	Sacituzumab govitecan
Target	HER2	Trop2
Subtype	HER2-Pos (3+ IHC, FISH+) HER2-Low (1-2+ IHC, FISH-Neg)	TNBC ER-Pos, HER2-Neg
Dose	5.4 mg/kg q21d	10 mg/kg IV D1,8 q21d
Payload	SN-38 Topo I inhibitor	Govitecan Topo I inhibitor
Payload:Ab ratio	8	7.6
Metabolism	UGT1A1 Substrate	UGT1A1 Substrate
Setting	2^{nd}-3^{rd} line	2^{nd}-3^{rd} line
Improved PFS	**HER2-Pos: Yes (vs. T-DM1)** **HER2-Low: Yes (vs. TPC)**	**TNBC: Yes (vs. TPC)** **ER-Pos, HE2-Neg: Yes (vs. TPC)**
Improved OS	**HER2-Pos: Yes (vs. T-DM1)** **HER2-Low: Yes (vs. TPC)**	**TNBC: Yes (vs. TPC)** **ER-Pos, HE2-Neg: Yes (vs. TPC)**
Most common toxicity	Neutropenia, nausea	Neutropenia, diarrhea, nausea/vomiting
Cost* (per 21 day cycle)	$11,020	$19,320

*Up-to-Date – accessed 11/1/20 (based on estimated cost for 70 kg individual)

Update on ER+ Breast Cancer

- Anti-estrogen therapy is a foundational component of therapy
  - Potentially curative when used as an “adjuvant” to local therapy
  - Prolongs survival in ER+ MBC
  - Current options includes SERMs (tamoxifen), SERDs (fulvestrant) and A.I.s
- CDK4/6 inhibitors are now standard component of first/second-line therapy
  - Improves OS, PFS, ORR in MBC
  - Improves IDFS/DRFS in adjuvant setting (impact on OS currently unknown)
- Targeting PIK3CA/AKT/M-TOR pathway a second-line therapeutic optioin
  - PIK3CA mutant (alpelisib) or non-mutant (everolimus)
  - Capivasertib may be a new options for PIK3CA pathway altered disease
- Novel oral SERDs (eg, elecestrant, others)
  - Modest efficacy in ESR1 mutant, endocrine therapy resistant MBC
- Antibody-drug conjugates
  - TDXd improves ORR, PFS, and OS in HER2-low disease
  - SC also has activity in heavily pretreated patient population