23rd Annual Hematology and Breast Cancer Update

Hormone Receptor Positive Disease

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January 22, 2023

Topics

- Low dose tamoxifen for prevention (TAM01)
- Adjuvant abemaciclib (MonarchE)
- Oral SERDS in 2L (EMERALD, SERENA2)
- AKT inhibition (Capitello-292)
- Endocrine therapy interruption for pregnancy (POSITIVE)

Atypia/DCIS – to treat or not to treat

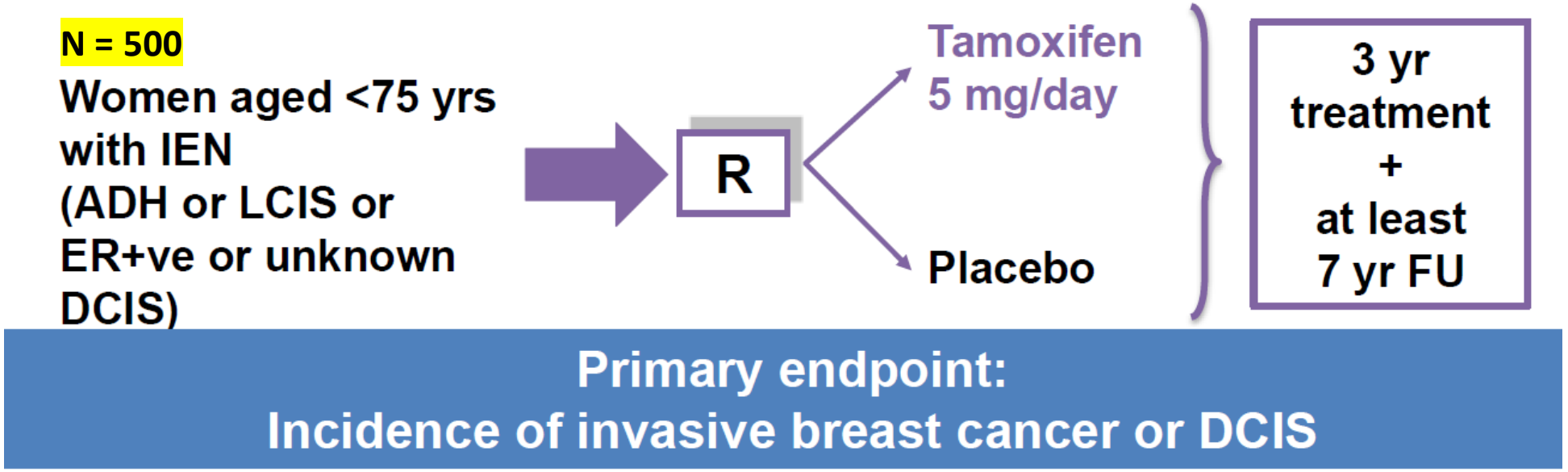
- Ongoing debate regarding the overdiagnosis and subsequent overtreatment of pure DCIS in the modern era (~1000 pts / yr in OR)
- Labeled as ‘cancer patients’
- Current risk perceptions are misleading and bias dialogue between clinicians and patients
- Autopsy studies median prevalence of DCIS 9%
  - Age >40 range 7-39%,
  - Invasive breast cancer 1%
- DCIS diagnosed age <40 do pose an increased risk of breast cancer specific mortality (detected by symptomatic event, mass, bloody discharge)

1) Welch Ann of Int Med 1997

‘Baby TAM’: Tamoxifen 5mg Long-term follow-up

5y follow-up (DeCensi JCO 2019)

- **ASCO and USPSTF guidelines for low-dose tamoxifen for high risk lesions**
- **NCCN if symptomatic or unwilling/unable to take full dose**



- 500 participants enrolled from 14 centers in Italy
- Visit and QoL every 6 months for 3 yrs, Mx every year for 10 yrs

DCIS ~70% (~30% HR unk)
ADH ~20%
LCIS ~10%

Premenopausal ~40%
BMI 25

BCS 80%

‘Baby TAM’: Key patient characteristics

Premenopausal 40%
BMI 25

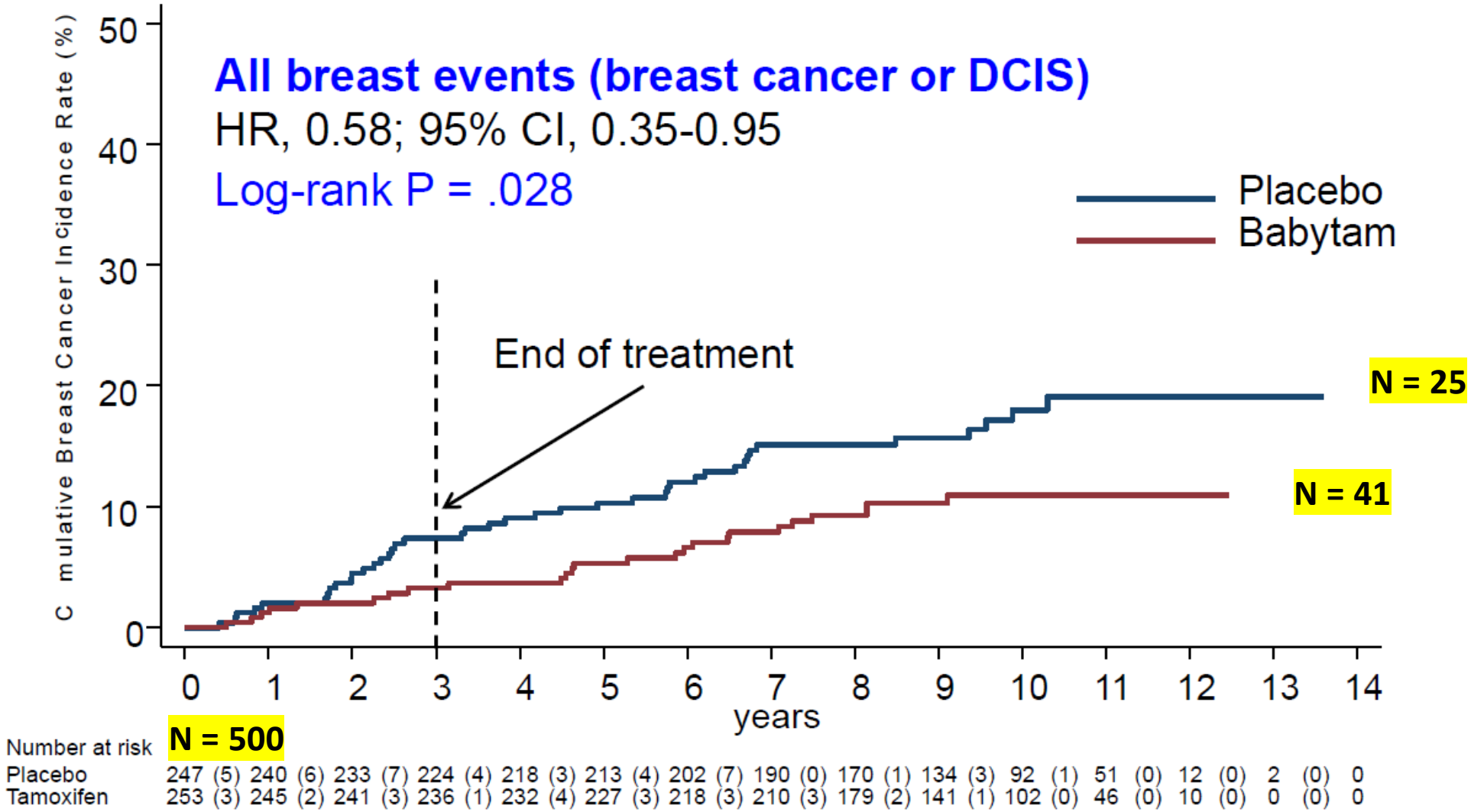
DCIS 70%
- ~30% HR unk
- ~20% high grade

ADH 20%
LCIS 10%

Breast conservation 80%
Radiation 45%
Mastectomy 20%

‘Baby TAM’: Tamoxifen 5mg Long-term follow-up

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

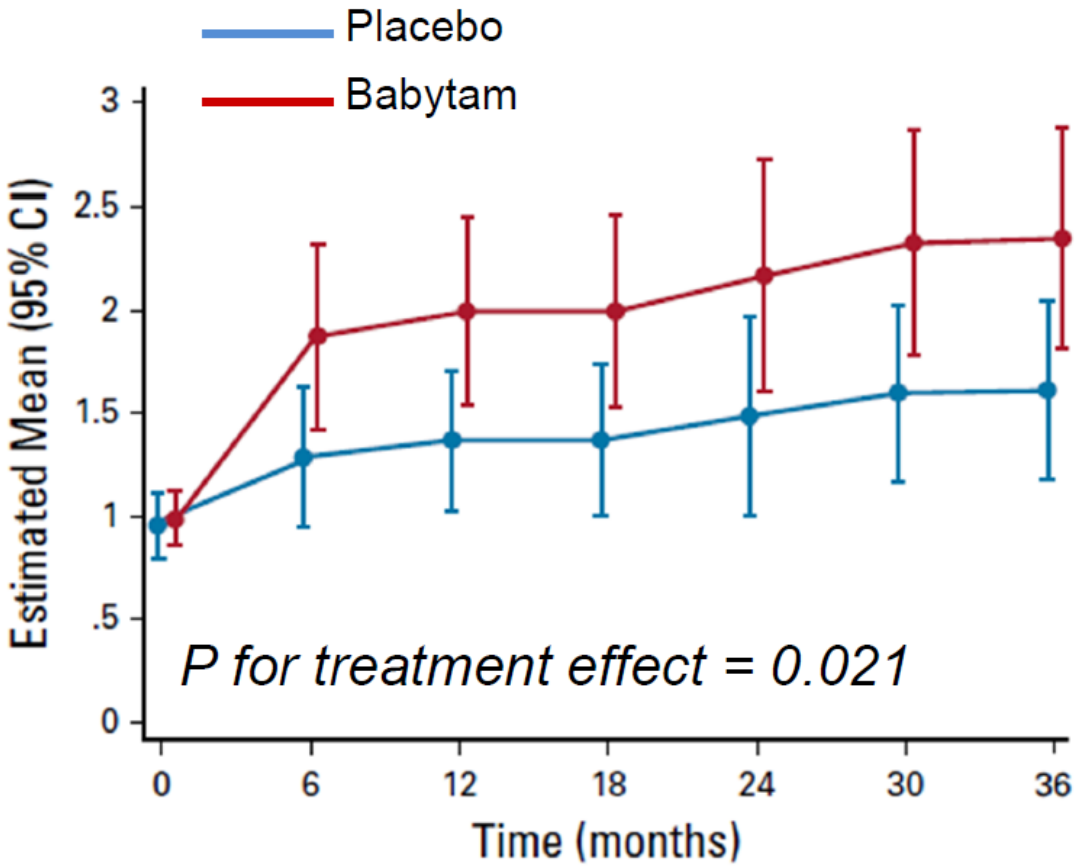


Main characteristics of breast events

	Tamoxifen (N=25)	Placebo (N=41)	p-value
Invasiveness, *n*			0.38
Invasive	21	30	
DCIS	4	11	
Site of recurrence, *n*			0.35
Ipsilateral	16	23	
Contralateral	6	16	
Distant	3	2	
Tumor stage, *n*			0.19
Tis	4	11	
T1	15	23	
T2-4	2	6	
Tx	4	1	
Nodes, *n*			0.89
Node-negative	21	33	
Node-positive	2	5	
Molecular phenotype, *n*			
Luminal	6	12	0.78
HER2+	15	22	0.80
Triple negative	0	3	0.28
Ki-67 %, *median (IQR)*	17 (11-30)	20 (13-30)	0.57

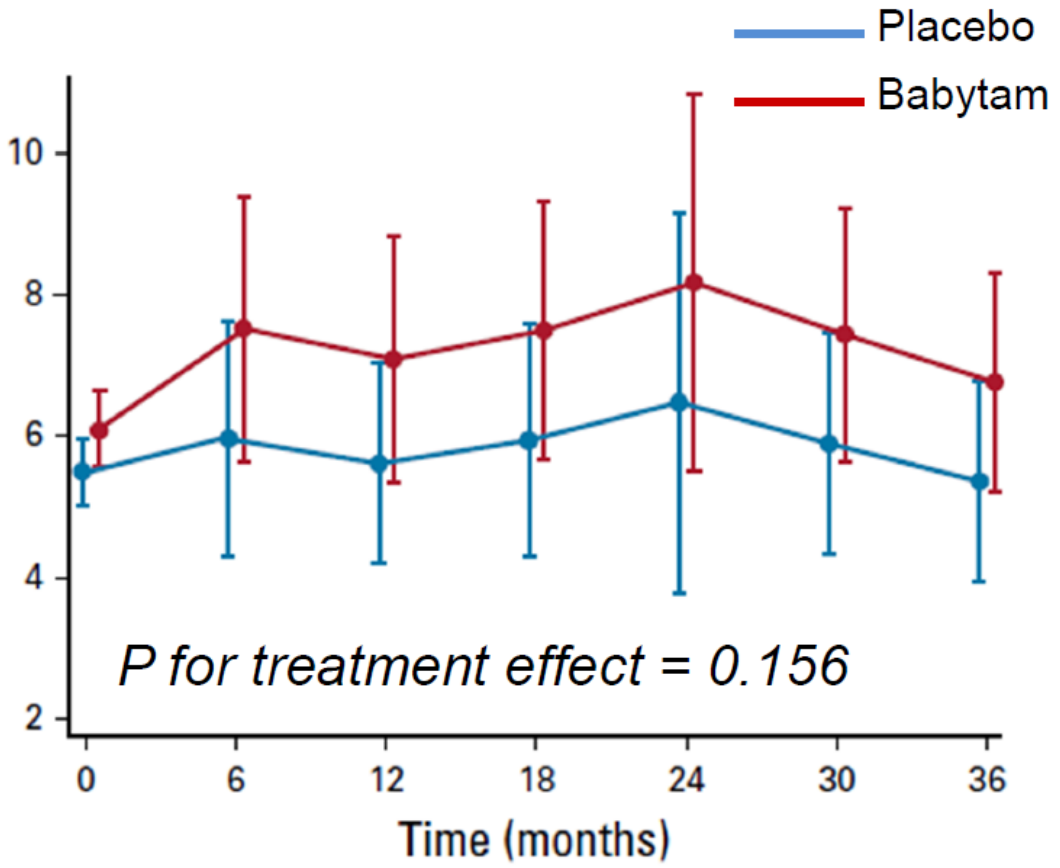
Symptoms

Daily hot flashes frequency



Daily hot flashes score

Frequency by Intensity



DeCensi et al. *J Clin Oncol.* 37(19):1629-1637, 2019

Adverse events

	Tamoxifen N=249	Placebo N=246	P Value
Adverse Events, n			
Endometrial cancer	1	0	1.0
Other neoplasms	16	9	0.22
Deep vein thrombosis or pulmonary embolism	1	1	1.0
Superficial phlebitis	2	0	0.50
Coronary heart disease	2	2	1.0
Bone fracture	4	2	0.69
Cataract	5	5	1.00
Endometrial polyps	20	13	0.28
Death from other causes	5	2	0.45
Death from breast cancer	1	2	0.62
Other serious adverse events	3	6	0.34

When to use baby tam

- DCIS
  - Low risk features
    - Grade low-int, <2.5cm, neg margins, unifocal, RT
  - Intolerant of tamoxifen 20mg
- ADH, LCIS, ALH
- Young women with prior chest RT
- BRCA2 and moderate penetrance gene carriers (PALB2, CHEK2, ATM)

Case

- 52yo premenopausal female with screen detected intermediate grade DCIS, spanning 1.8cm on lumpectomy specimen
- DCISionRT – low risk ($3416)
- After discussion with rad onc decision to defer radiation
- Patient was on HRT prior to diagnosis
- She sees medical oncology in clinic
- MSKCC nomogram without RT/ET 5y = 9%, 10y = 15%, (4% and 7% respectively with ET)
- Radiation oncology – if no endocrine therapy then will possibly radiate
  - DCISionRT nor Oncotype DCIS DX score is not designed to predict endocrine therapy benefit

Adjuvant abemaciclib monarchE: OS interim analysis and 4y efficacy outcomes

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

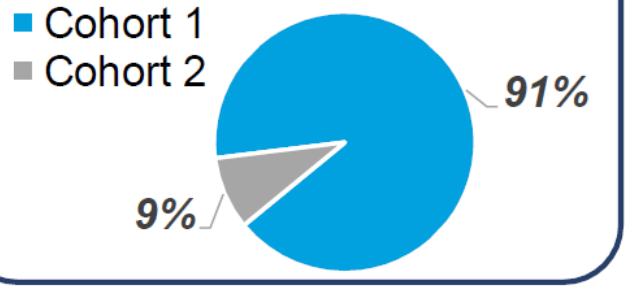
Abemaciclib
(150mg twice daily)
+
Endocrine Therapy: AI or tamoxifen

Endocrine Therapy: AI or tamoxifen

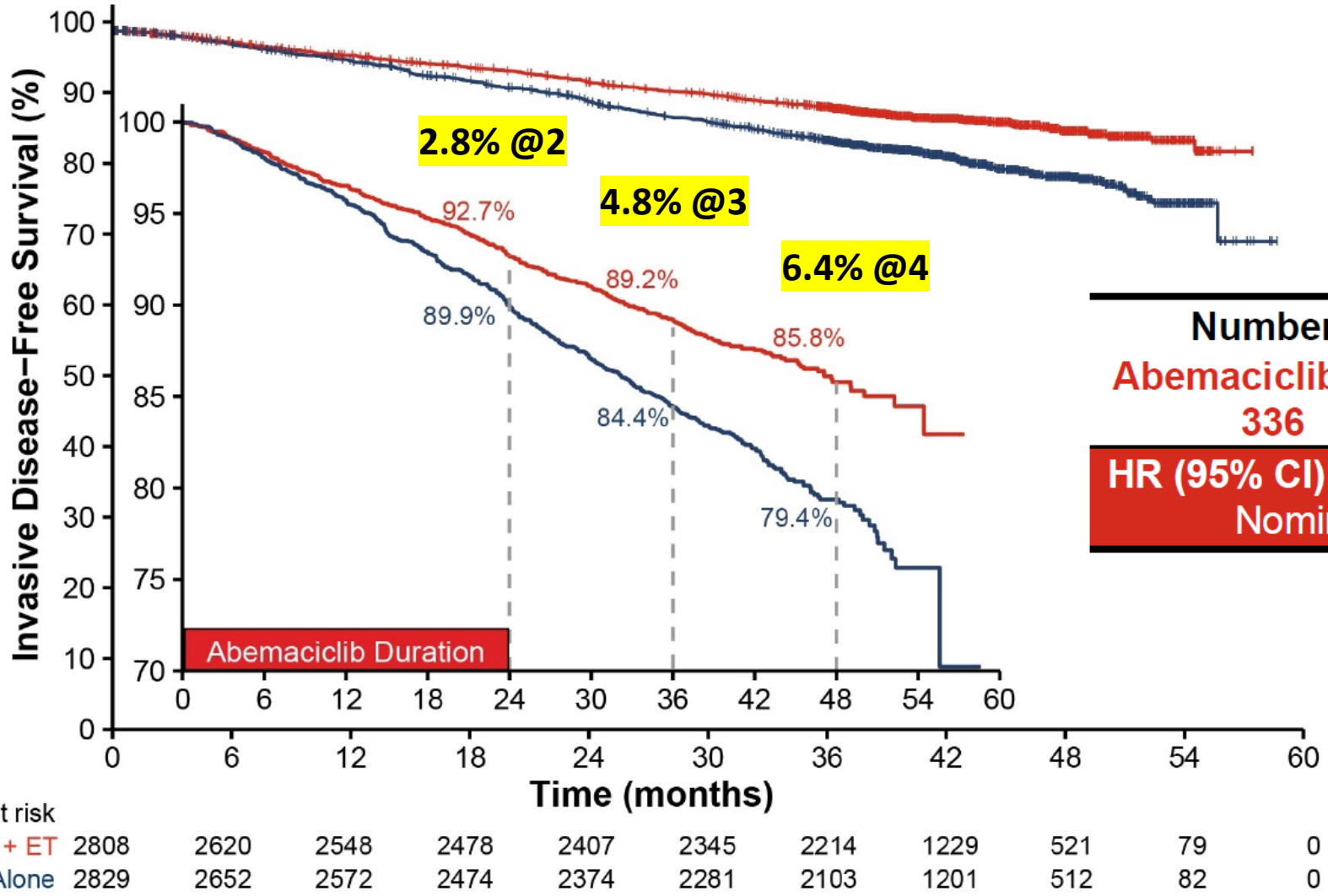
Follow-up period
Endocrine Therapy
3-8 years as clinically indicated

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

ITT Population



Adjuvant abemaciclib: iDFS @ 4 years



Number of IDFS events

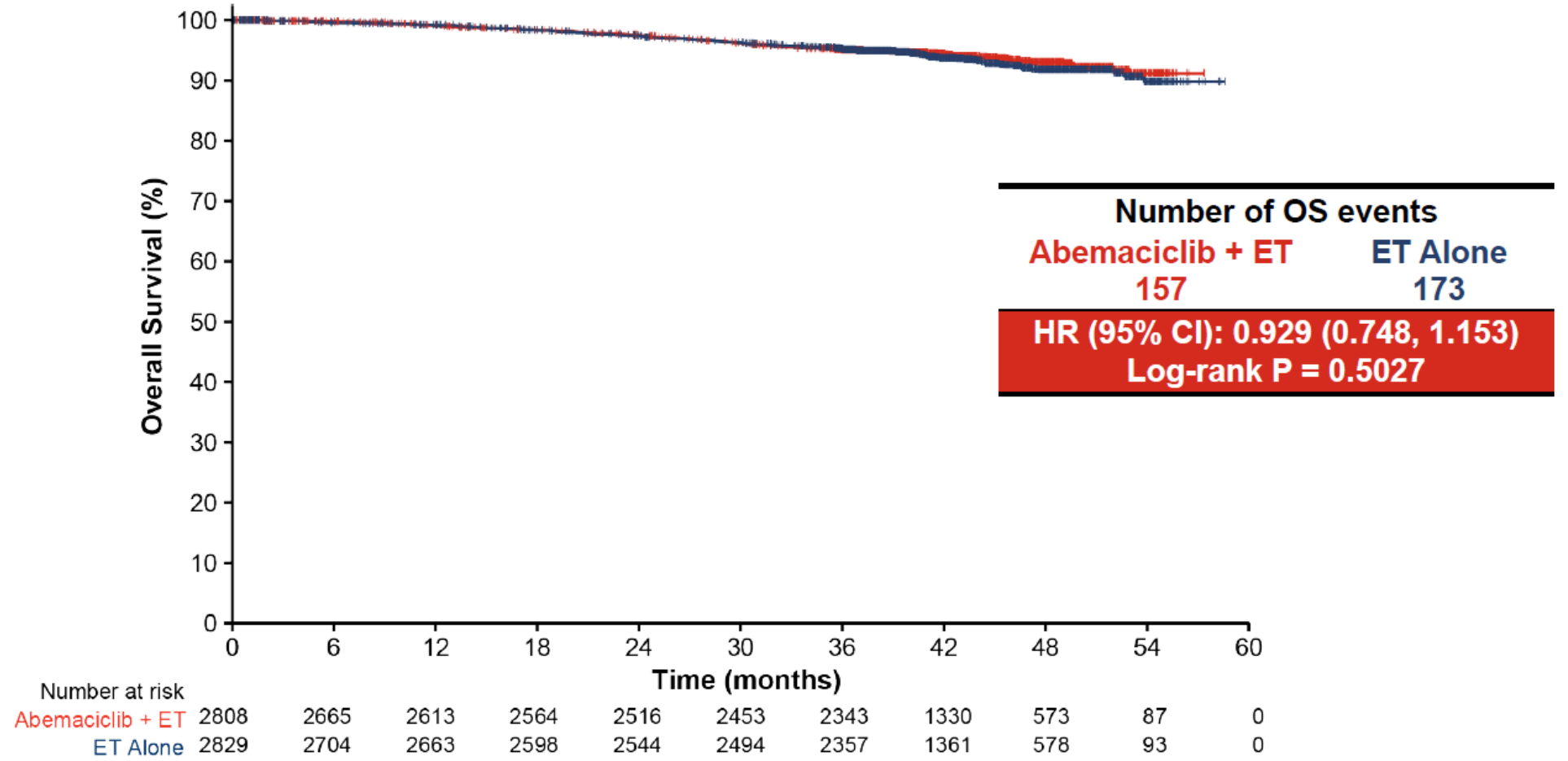
Abemaciclib + ET	ET Alone
336	499

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)

Adjuvant abemaciclib: overall survival

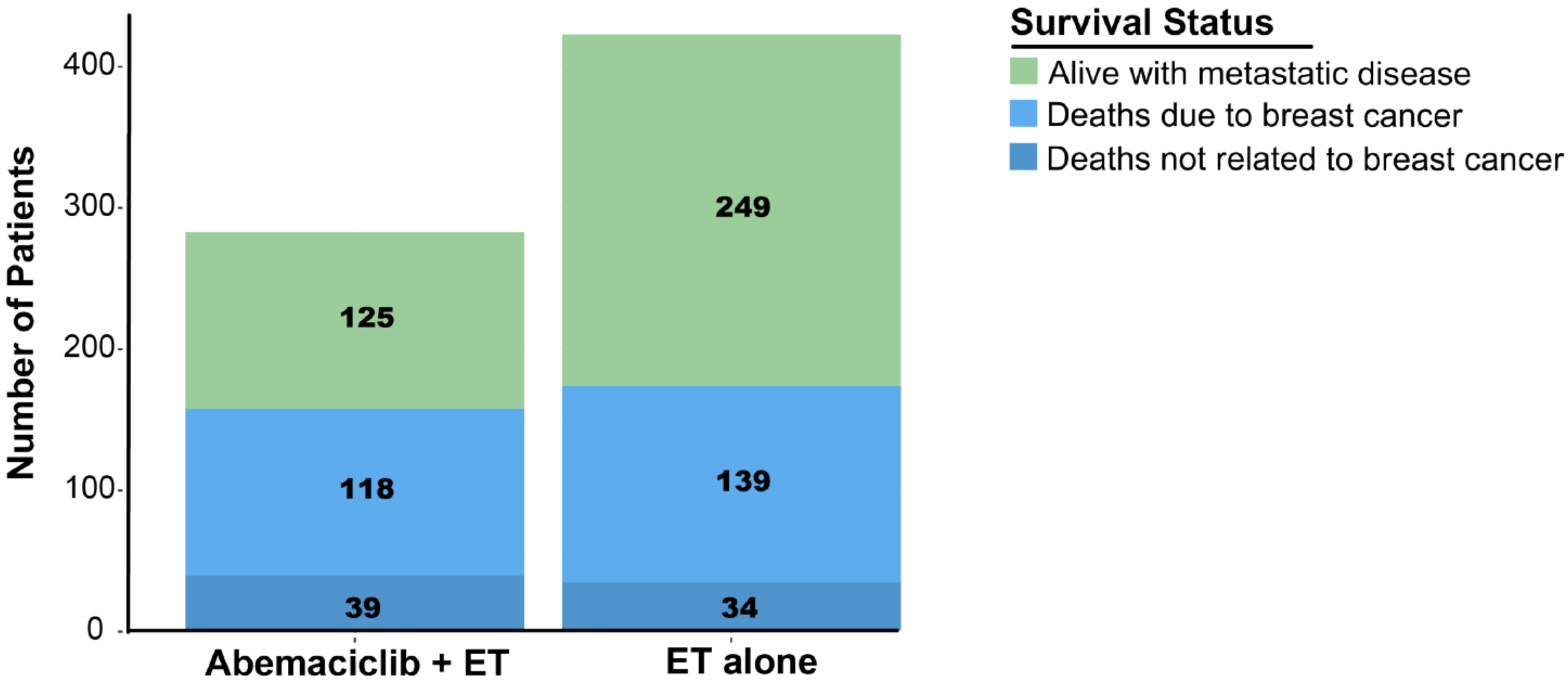
OS Data Remain Immature in ITT



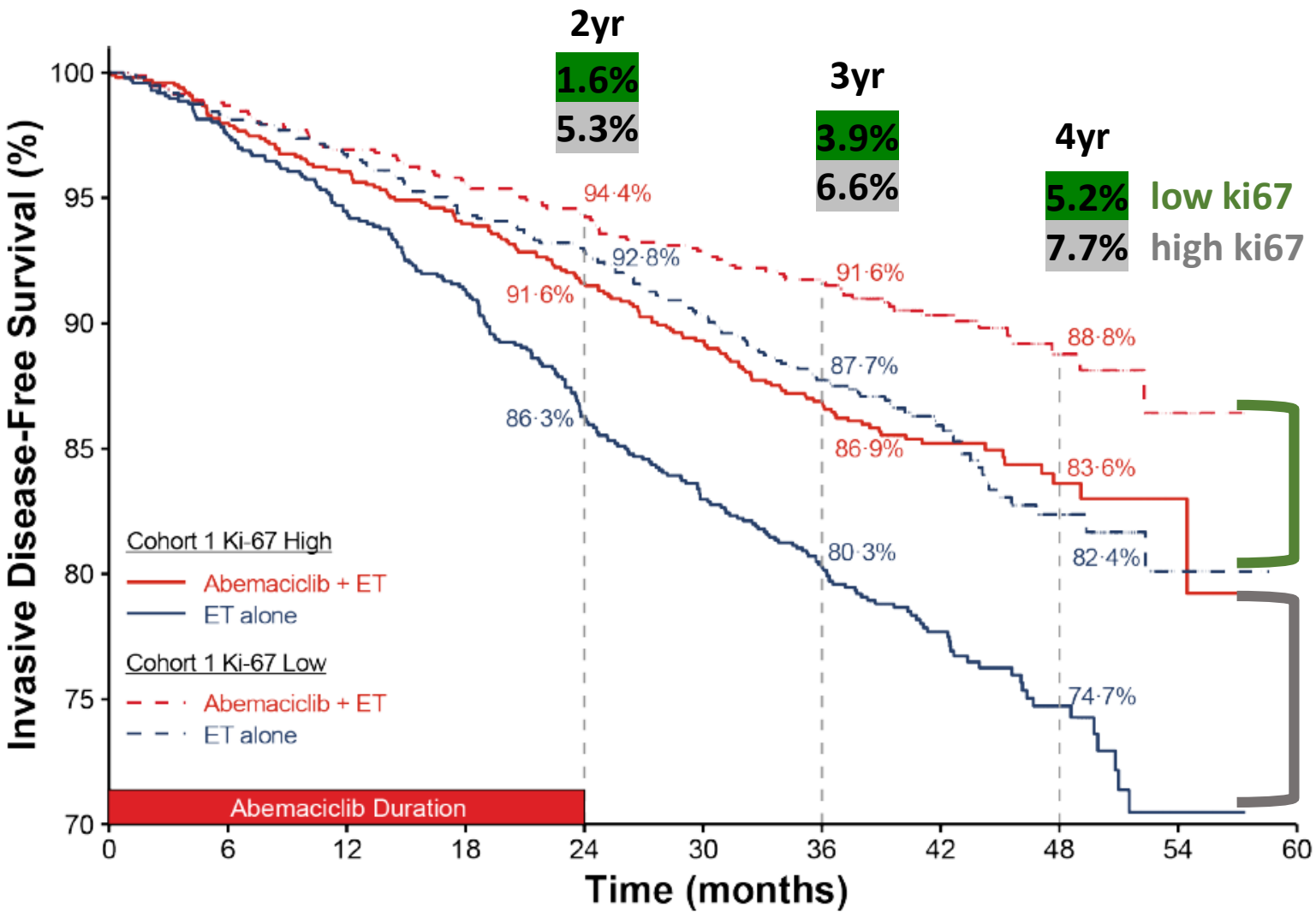
Fewer deaths (157 vs 173) were observed in the abemaciclib plus ET group versus the ET group

Adjuvant abemaciclib: metastatic disease

Fewer Patients with Metastatic Disease in the Abemaciclib arm



Adjuvant abemaciclib: Ki-67 is prognostic but not predictive



Cohort 1: low ki67
≥ 4 ALN
1-3 ALN + [G3, T ≥ 5cm]

Cohort 1: high Ki67
≥ 4 ALN
1-3 ALN + [G3, T ≥ 5cm]

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

Initial adjuvant abemaciclib approval

- First approval in 16 years for early-stage HR+ breast cancer
- Immature OS analysis, showed a potential detriment in survival in pts with Ki67 ≤ 20% (OS HR >1)
  - Ad hoc analysis of cohort 2 (517 pts) small number of events making difficult to interpret iDFS benefit
- FDA: limited to cohort 1 and **Ki67 ≥ 20%** where iDFS remained consistent and no potential detriment in OS was observed
- NCCN: ≥4 ALN, or 1–3 ALN with one or more of the following: G3, T>5cm, **or Ki67 ≥20**

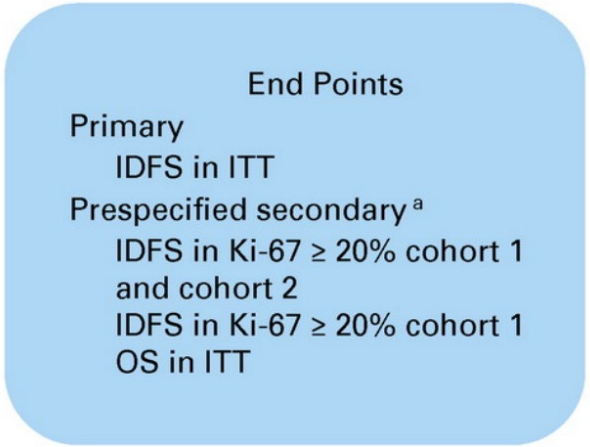
Cohort 1:

≥ 4 ALN

1-3 ALN + [G3, T ≥ 5cm]

Cohort 2:

Ki67 ≥ 20% + 1-3 ALN

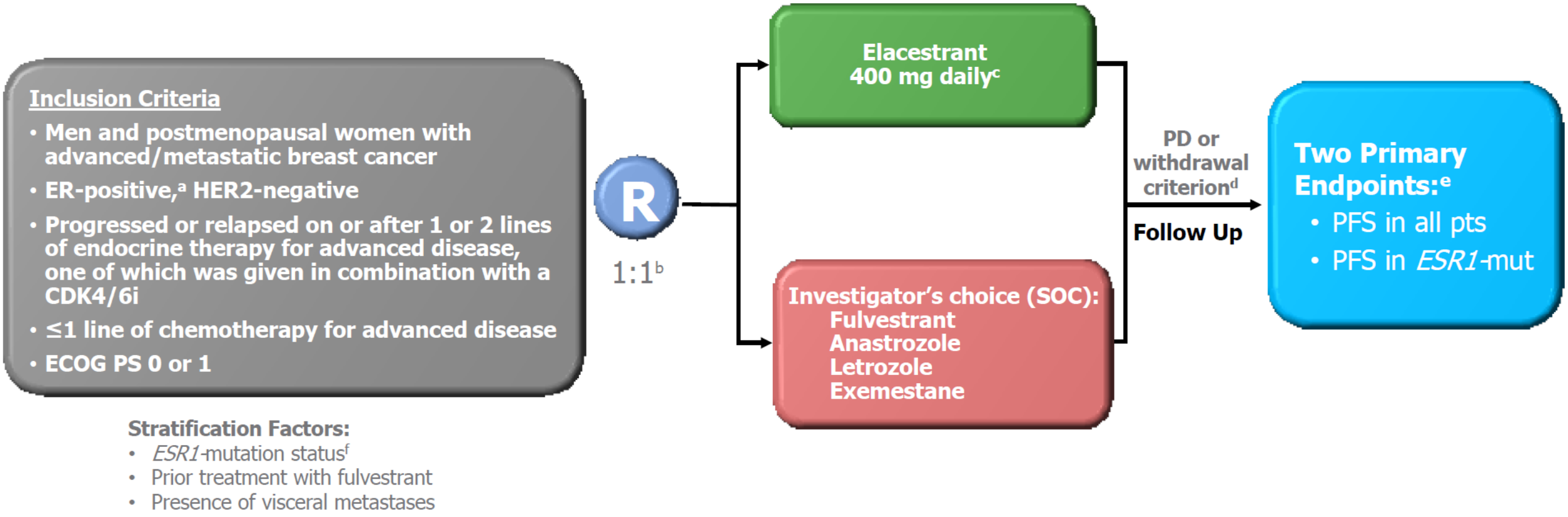


Royce JCO 2022

Oral SERDS: EMERALD & SERENA2

	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

Phase III EMERALD



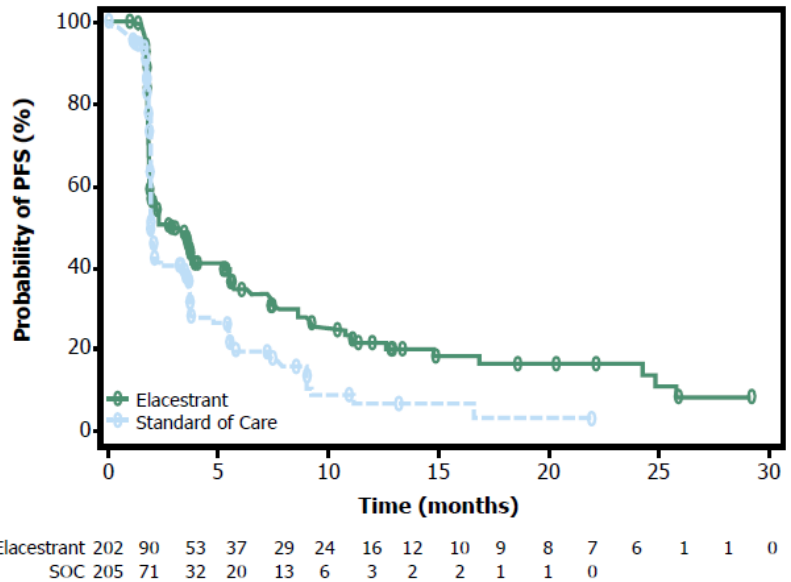
EMERALD: Baseline Characteristics

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 AI Tamoxifen	 70 (29.3) 193 (80.8) 19 (7.9)	 27 (23.5) 101 (87.8) 9 (7.8)	 75 (31.4) 194 (81.2) 15 (6.3)	 28 (24.8) 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

EMERALD: PFS by duration of CDK4/6 in IIT

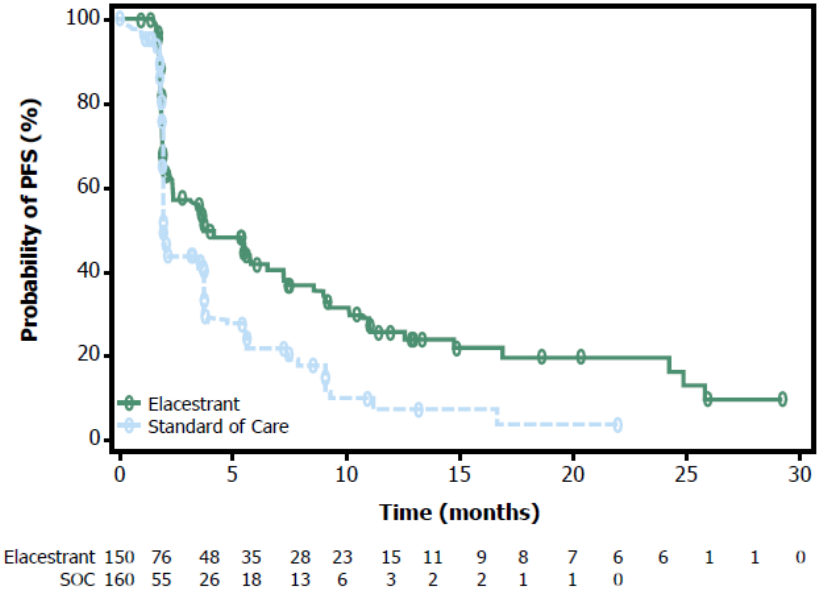
At least 6 mo CDK4/6i



	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)	

1.6m

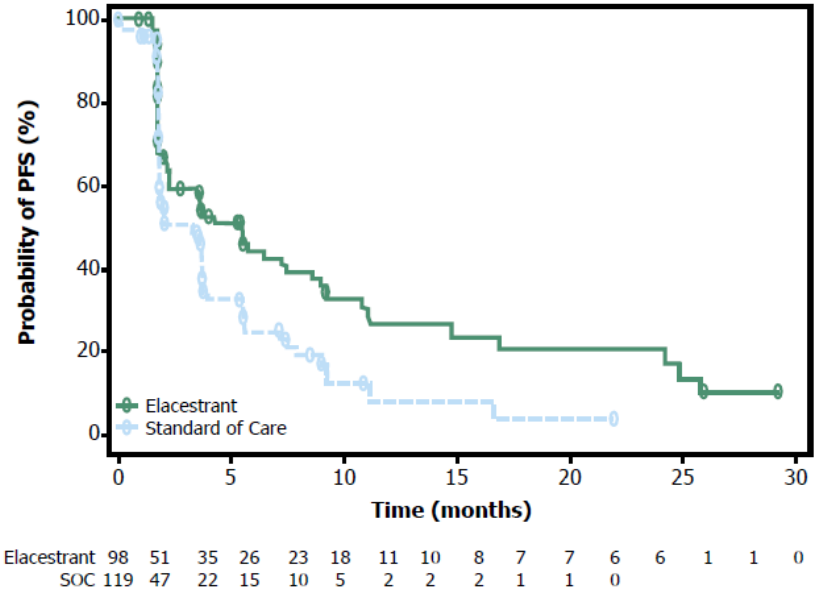
At least 12 mo CDK4/6i



	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)	

1.87m

At least 18 mo CDK4/6i

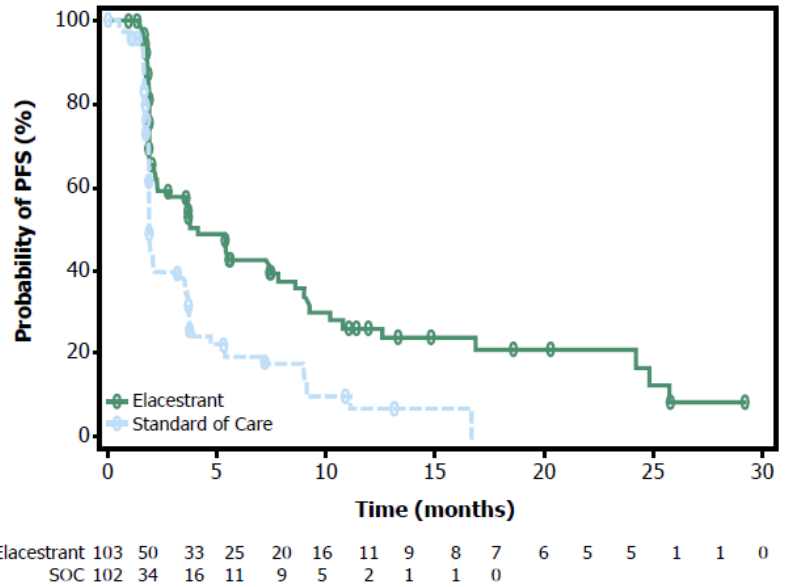


	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**5.45** (2.33 - 8.61)	**3.29** (1.87 - 3.71)
PFS rate at 12 months, % (95% CI)	26.70 (15.61 - 37.80)	8.23 (0.00 - 17.07)
Hazard ratio (95% CI)	**0.703** (0.482 - 1.019)	

2.16m

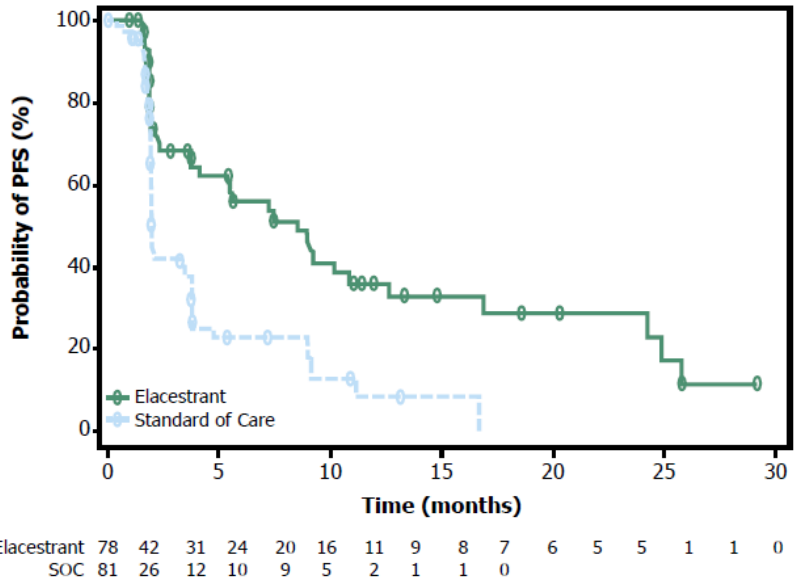
EMERALD: ESR1-mt PFS by duration of CDK4/6

At least 6 mo CDK4/6i



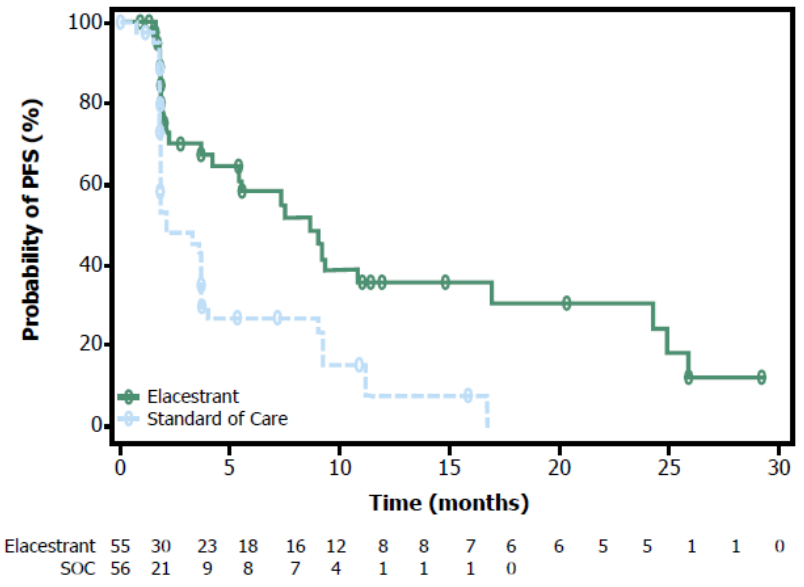
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

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)	

EMERALD: Safety

Updated safety data were consistent with previously reported results:

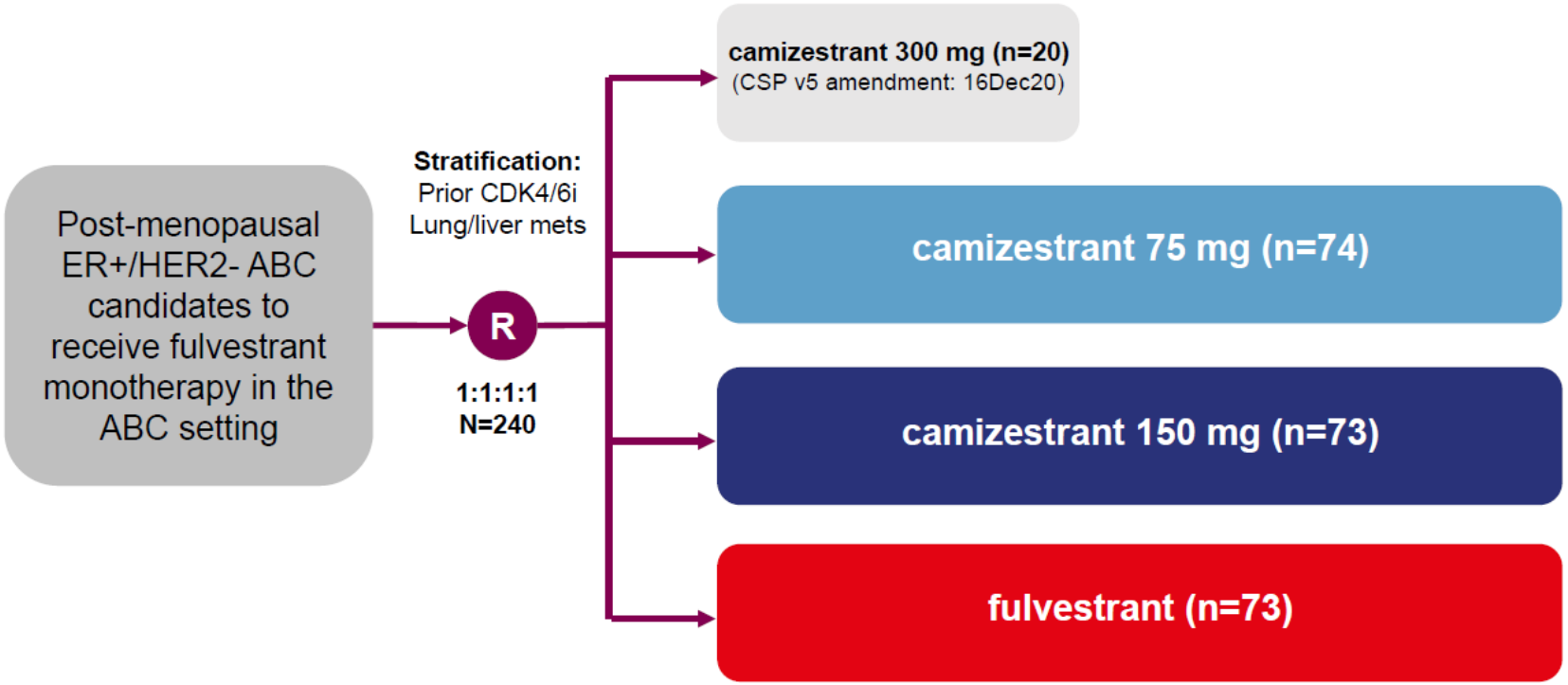
- Most adverse events (AEs), including nausea, were grade 1 and 2, and no grade 4 treatment-related AEs (TRAEs) were reported.
- Only 3.4% of patients receiving elacestrant and 0.9% receiving SOC discontinued therapy due to any TRAE.
- No deaths assessed as treatment-related were reported in either arm.
- No hematologic safety signal was observed, and none of the patients in either treatment arm had sinus bradycardia.

Nausea Summary	Elacestrant (n=237)	SOC (n=230)
Grade 3 nausea, n (%)	6 (2.5%)	2 (0.9%)
Dose-reduction rate due to nausea, n (%)	3 (1.3%)	Not applicable
Discontinuation rate due to nausea, n (%)	3 (1.3%)	0 (0%)
Antiemetic use	8%	10.3% (AI) 1.3% (Ful)

Phase II SERENA-2: Camizestrant

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

SERENA-2: Camizestrant

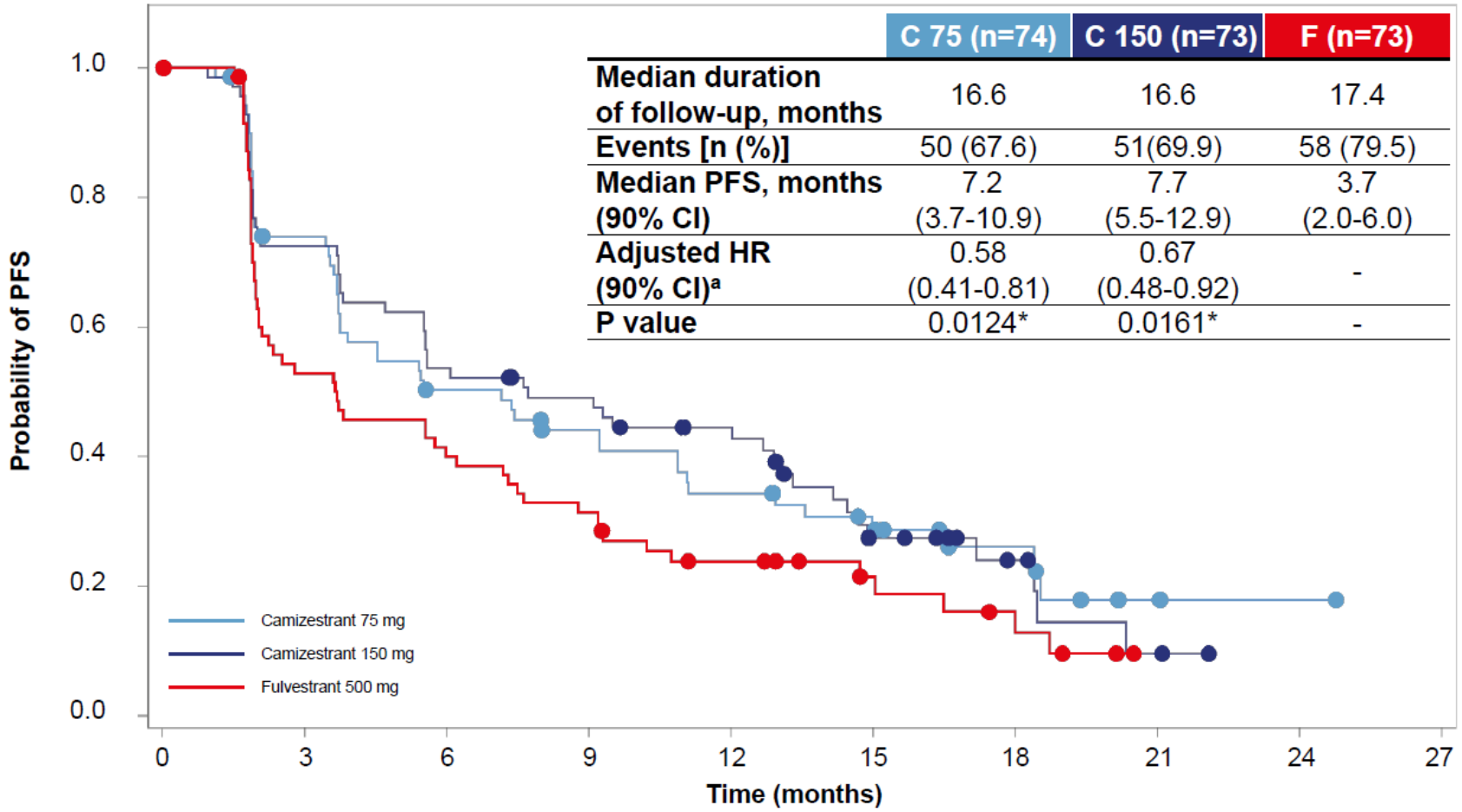
	C 75 (n=74)	C 150 (n=73)	F (n=73)	Total (n=240)
Age (median, range)	61.0 (37-89)	60.0 (42-84)	60.0 (35-84)	60.0 (35-89)
Gender, F (%)[a]	100	100	100	100
Race, White (%)	95.9	95.9	89.0	94.2
ER+ (%)	100	100	100	100
PgR+ (%)	81.1	84.9	79.5	79.6
ECOG 0 (%)	62.2	57.5	58.9	58.8
Lung/liver metastasis Y (%)	58.1	58.9	58.9	58.3
Liver metastasis (%)	31.1	41.1	47.9	40.8
Bone only disease (%)	14.9	19.4	17.8	17.6
*ESR1*m detectable (%)[b]	29.7	35.6	47.9	36.7
D538G	18.9	19.2	31.5	22.9
Y537N	14.9	15.1	15.1	13.8
Y537S	6.8	13.7	19.2	12.5
E380Q	9.5	8.2	8.2	8.3
L536H	1.4	8.2	4.1	4.6
Y537C	4.1	4.1	2.7	3.3

	C 75 (n=74)	C 150 (n=73)	F (n=73)	Total (n=240)
CT adjuvant, Y (%)	54.1	53.4	52.1	52.1
CT in ABC, Y (%)	21.6	12.3	26.0	19.2
ET overall, lines (%)				
0	1.4	1.4	0	0.8
1	81.1	72.6	76.7	77.1
2	16.2	24.7	19.2	20.0
3	1.4	1.4	4.1	2.1
ET adjuvant, Y (%)	66.2	71.2	60.3	66.7
AI	40.5	35.6	31.5	35.8
SERM	32.4	45.2	43.8	41.7
ET in ABC, lines (%)				
0	37.8	28.8	26.0	31.3
1	62.2	71.2	74.0	68.8
AI	55.4	67.1	67.1	63.3
SERM	6.8	2.7	6.8	5.0
Prior CDK4/6i Y (%)[c]	51.4	50.7	50.7	49.6
Palbociclib	21.6	31.5	30.1	27.9
Ribociclib	23.0	19.2	16.4	18.3
Abemaciclib	5.4	1.4	4.1	3.8

[a]All post-menopausal women; [b]*ESR1*m assessed in plasma samples at screening (GuardantOMNI™) and Cycle 1 Day 1 (Guardant360®), *ESR1*m defined as E380Q, V422del, S463P, L536H/P/R, Y537C/D/N/S, D538G, individual mutations present in >2% total cases reported; [c]Missing or not specified in 3 patients

ABC: advanced breast cancer; AI: aromatase inhibitor; C: camizestrant; CDK4/6i: CDK4/6 inhibitor; CT: chemotherapy; ECOG: Eastern Cooperative Oncology Group; ER: estrogen receptor; *ESR1*m: mutation in estrogen receptor 1 gene; ET: endocrine therapy; F: female; PgR: progesterone receptor; SERM: selective estrogen receptor modulator (tamoxifen or toremifene)

SERENA-2: 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

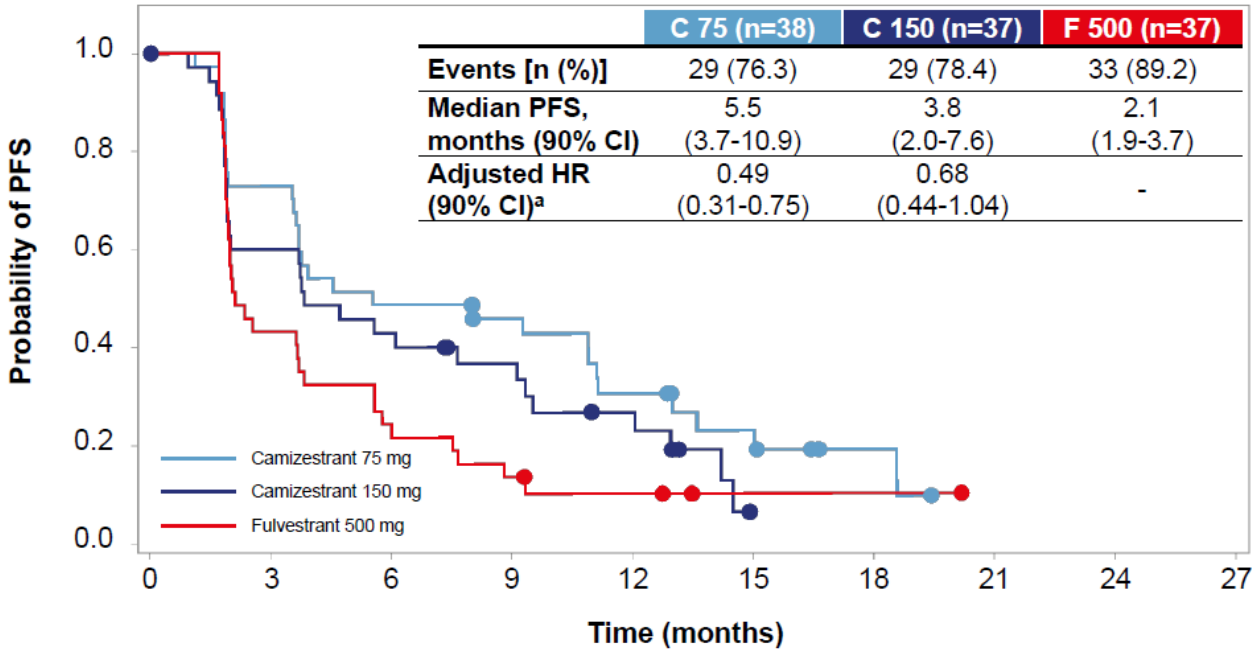
CDK4/6i: CDK4/6 inhibitor; CI: confidence interval; HR: hazard ratio; PFS: progression-free survival

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

SERENA-2: PFS by based on prior CDK4/6

Prior CDK4/6i

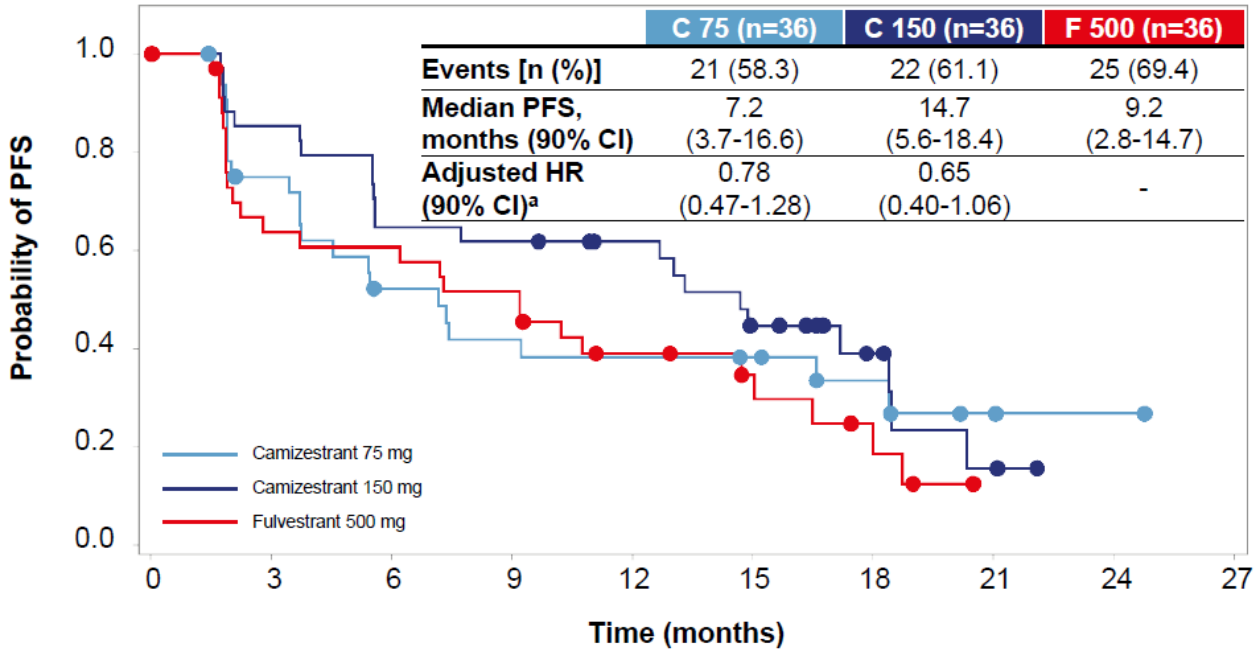
	C 75 (n=38)	C 150 (n=37)	F 500 (n=37)
Events [n (%)]	29 (76.3)	29 (78.4)	33 (89.2)
Median PFS, months (90% CI)	5.5 (3.7-10.9)	3.8 (2.0-7.6)	2.1 (1.9-3.7)
Adjusted HR (90% CI)[a]	0.49 (0.31-0.75)	0.68 (0.44-1.04)	-



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		

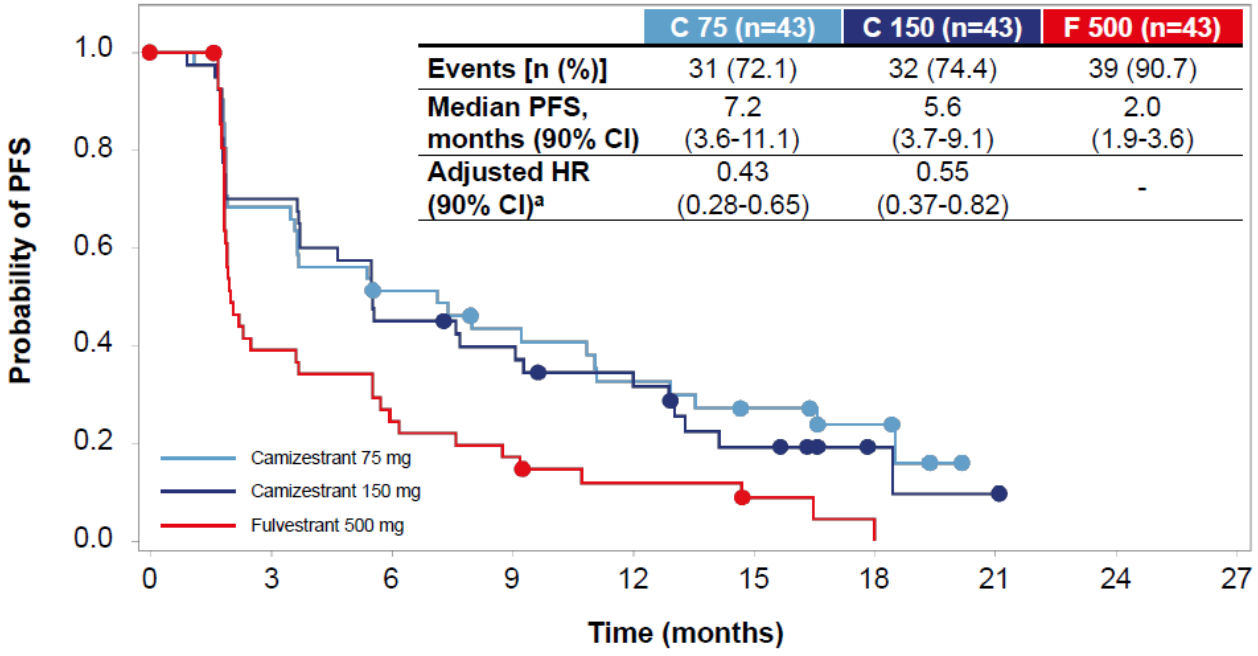
- In the sub-population of patients previously treated with CDK4/6i + endocrine therapy, camizestrant at both doses produces a clinically meaningful improvement in PFS over fulvestrant

[a]HRs adjusted for liver/lung metastases

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

SERENA-2: PFS by based on visceral mets

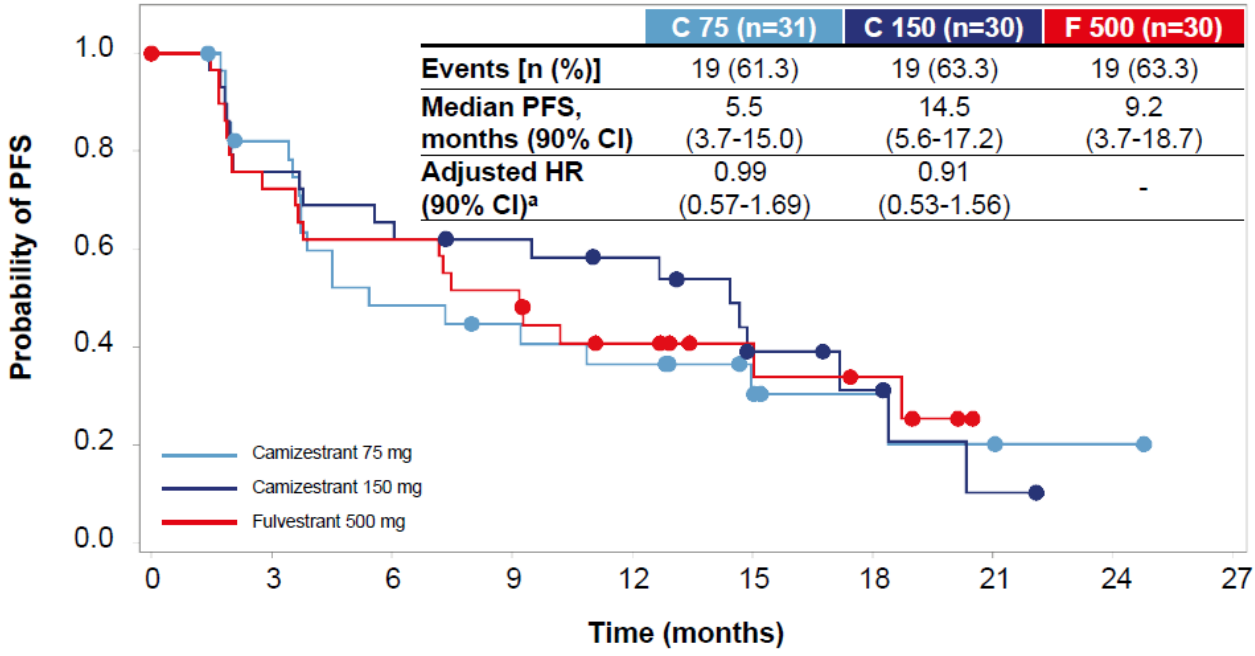
Presence of lung and/or liver metastases



	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)	-

C 75	43	28	20	16	12	9	4	0		
C 150	43	28	18	15	12	6	2	1	0	
F	43	16	10	7	4	2	1	0		

No lung or liver metastases



	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)	-

C 75	31	22	13	11	9	5	3	2	1	0
C 150	30	22	19	17	13	6	4	1	0	
F	30	21	18	15	10	6	4	0		

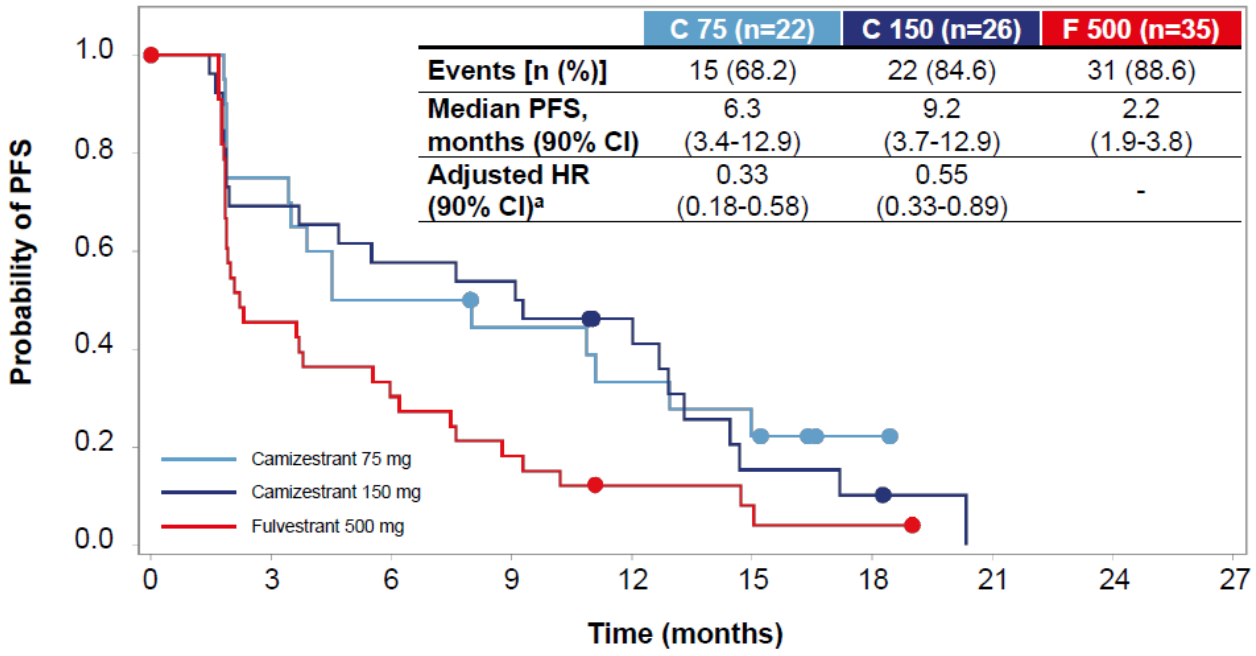
- In the sub-population of patients with lung and/or liver metastases, camizestrant at both doses produces a clinically meaningful improvement in PFS over fulvestrant

[a]HRs adjusted for prior use of CDK4/6i

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

SERENA-2: PFS by based on ESR1m

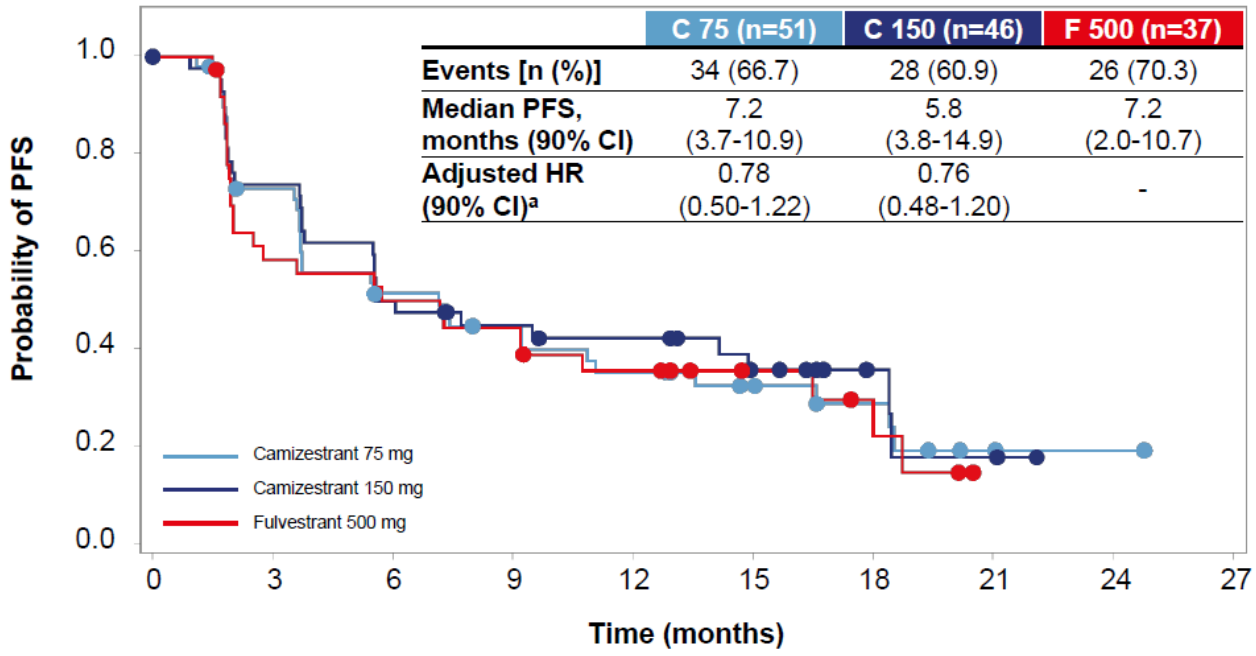
*ESR1*m detectable at baseline



	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)	-

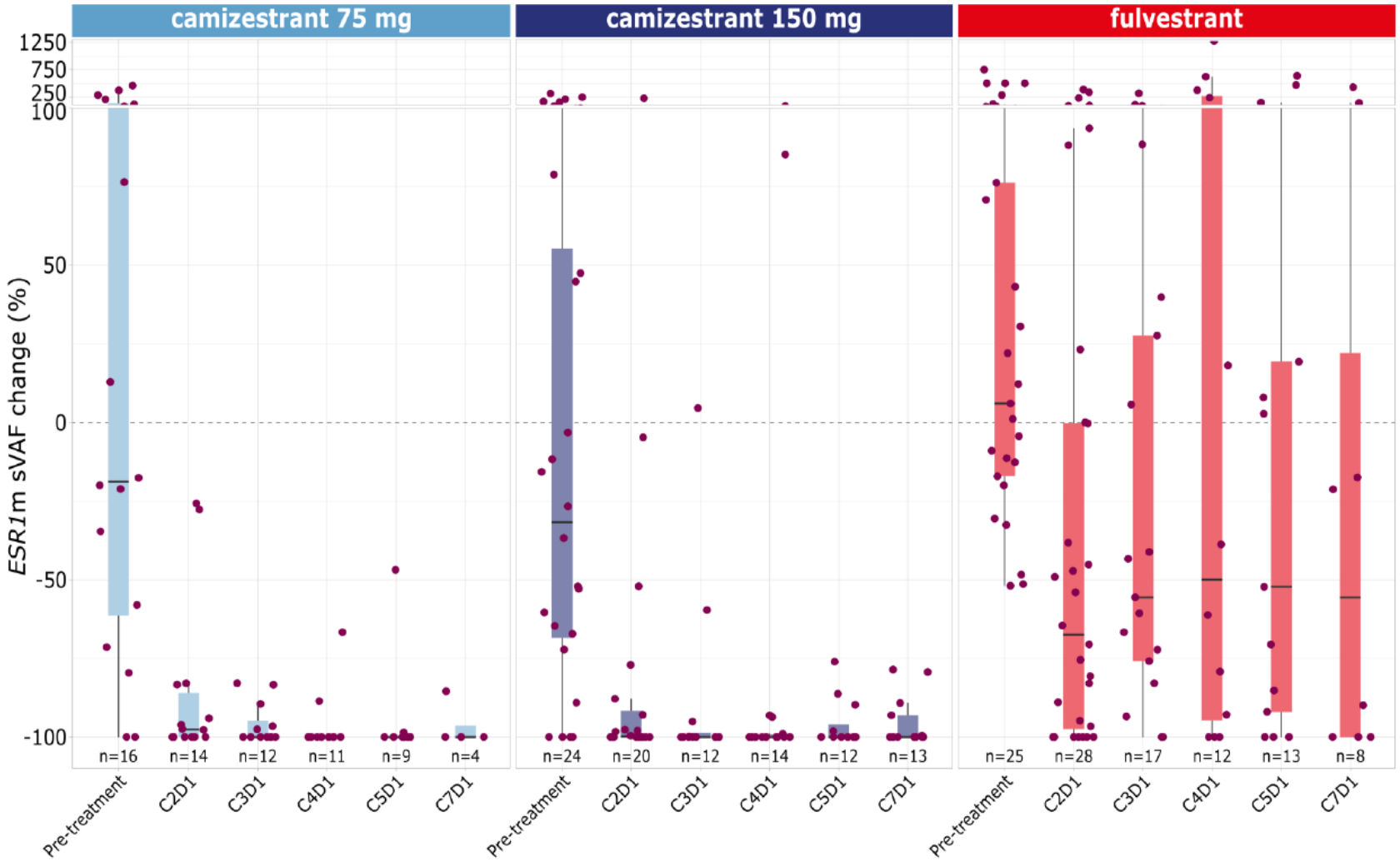
C 75	51	34	23	19	15	10	6	2	1	0
C 150	46	31	21	17	15	9	4	2	0	
F	37	21	18	16	11	6	4	1	0	

- 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

SERENA-2: Changes in ESR1mt VAF



- Treatment with camizestrant 75 and 150 mg reduced the level of *ESR1*m ctDNA to undetectable or near undetectable levels by Cycle 2 Day 1 and maintained this to Cycle 7 Day 1
- Fulvestrant also reduced levels of *ESR1*m ctDNA, but not to the same extent as camizestrant

*ESR1*m classed as E380Q, V422del, S463P, L536H/P/R, Y537C/D/N/S, D538G. Pre-treatment = % change in *ESR1*m sVAF from screening to Cycle 1 Day 1, CXD1 = % change from Cycle 1 Day 1 to Cycle X Day 1

ctDNA: circulating tumor DNA; *ESR1*m: mutation in estrogen receptor 1 gene; *ESR1*m sVAF: Summed variant allele frequency of qualifying *ESR1*m

SERENA-2: Safety

	C 75 (n=74)	C 150 (n=73)	C 300 (n=20)	F 500 (n=73)
Total duration, months, mean (SD)	8.27 (6.59)	8.91 (6.78)	9.26 (8.19)	7.34 (6.09)
Any treatment-emergent AE (TEAE), n (%)	57 (77.0)	66 (90.4)	19 (95.0)	50 (68.5)
Any treatment-related AE (TRAE), n (%)	39 (52.7)	49 (67.1)	14 (70.0)	13 (17.8)
CTCAE Grade 3 or higher, n (%)	1 (1.4)	2 (2.7)	1 (5.0)	1 (1.4)
serious, n (%)	3 (4.1)	2 (2.7)	1 (5.0)	0
fatal	0	0	0	0
leading to discontinuation of treatment, n (%)	2 (2.7)	0	0	0
TEAE leading to dose reduction, n (%)	1 (1.4)	9 (12.3)	4 (20.0)	0
TEAE leading to dose interruption, n (%)	11 (14.9)	16 (21.9)	4 (20.0)	3 (4.1)
TRAE leading to dose interruption, n (%)	7 (9.5)	8 (11.0)	3 (15.0)	0
Median duration of dose interruption (days)	7.0	7.5	7.0	-

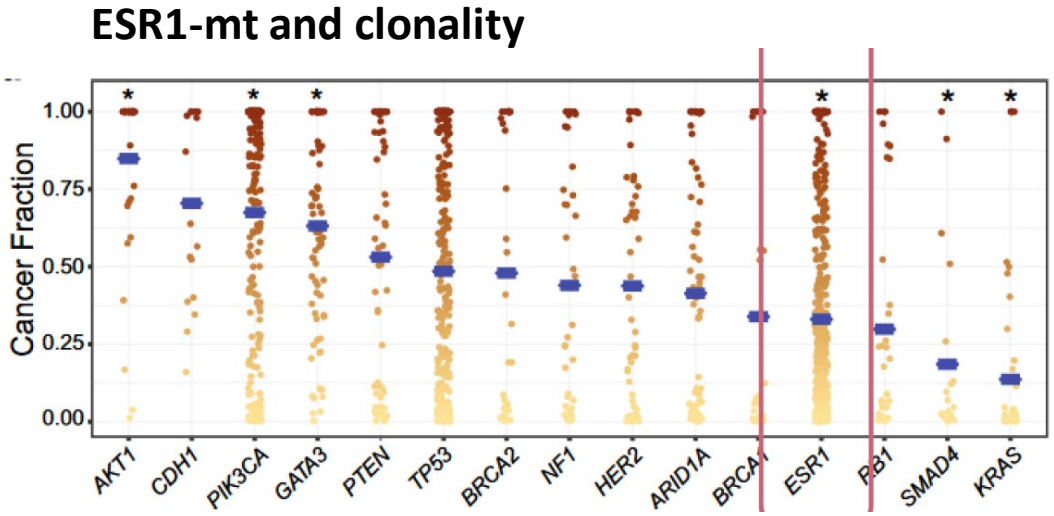
- TRAEs of Grade 3 or higher and TRAEs leading to discontinuation were infrequent across all treatment arms
- TRAEs leading to dose interruptions were numerically similar for camizestrant 75 and 150 mg, and of short duration
- All camizestrant doses are well tolerated

SERENA-2: Safety

AE, n (%)	C 75 (n=74)		C 150 (n=73)		C 300 (n=20)		F 500 (n=73)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any AE	57 (77.0)	9 (12.2)	66 (90.4)	16 (21.9)	19 (95.0)	3 (15)	50 (68.5)	10 (13.7)
Photopsia	9 (12.2)	0	18 (24.7)	0	7 (35.0)	0	0	0
(Sinus) bradycardia	4 (5.4)	0	19 (26.0)	0	8 (40.0)	0	0	0
Fatigue	4 (5.4)	0	13 (17.8)	1 (1.4)	4 (20.0)	0	3 (4.1)	0
Anemia	8 (10.8)	0	11 (15.1)	1 (1.4)	1 (5.0)	0	5 (6.8)	2 (2.7)
Asthenia	6 (8.1)	0	11 (15.1)	0	2 (10.0)	0	4 (5.5)	0
Arthralgia	3 (4.1)	0	9 (12.3)	1 (1.4)	2 (10.0)	0	2 (2.7)	0
AST increased	2 (2.7)	0	6 (8.2)	0	2 (10.0)	0	5 (6.8)	1 (1.4)
ALT increased	1 (1.4)	0	6 (8.2)	1 (1.4)	3 (15.0)	0	4 (5.5)	1 (1.4)
Covid-19	4 (5.4)	0	4 (5.5)	0	3 (15.0)	0	3 (4.1)	0
Diarrhea	4 (5.4)	0	4 (5.5)	0	3 (15.0)	1 (5.0)	2 (2.7)	1 (1.4)
Pain in extremity	1 (1.4)	0	4 (5.5)	1 (1.4)	2 (10.0)	0	3 (4.1)	0
Dyspepsia	1 (1.4)	0	3 (4.1)	0	2 (10.0)	0	1 (1.4)	0
Insomnia	1 (1.4)	0	3 (4.1)	0	2 (10.0)	0	1 (1.4)	0
Hyponatremia	0	0	3 (4.1)	1 (1.4)	2 (10.0)	0	1 (1.4)	1 (1.4)
Blood pressure increased	2 (2.7)	1 (1.4)	1 (1.4)	1 (1.4)	2 (10.0)	1 (5.0)	0	0
Cataract	2 (2.7)	0	0	0	2 (10.0)	0	0	0
Vitreous floaters	2 (2.7)	0	0	0	2 (10.0)	0	0	0

Summary of EMERALD (Elacestrant) & SERENA-2 (Camizestrant)

- 30-40% will have progression at 1st staging (25% if ESR1-mt)
  - Closer monitoring -- Tumor markers, ctDNA VAF, imaging?
- CDK progression <6-12m
  - Should they be treated with cytotoxics?
- Most appropriate for pts with ESR1-mts
  - At least as effective FUL in ESR1-wt
- Elacestrant up for FDA approval (EMERALD)
- Will drugs prevent ESR1-mt when given frontline?



Resistance driven by ESR1-mt
ESR1-mt that don't drive resistance
ESR1-wt with resistance

Kingston Nat Comm 2021

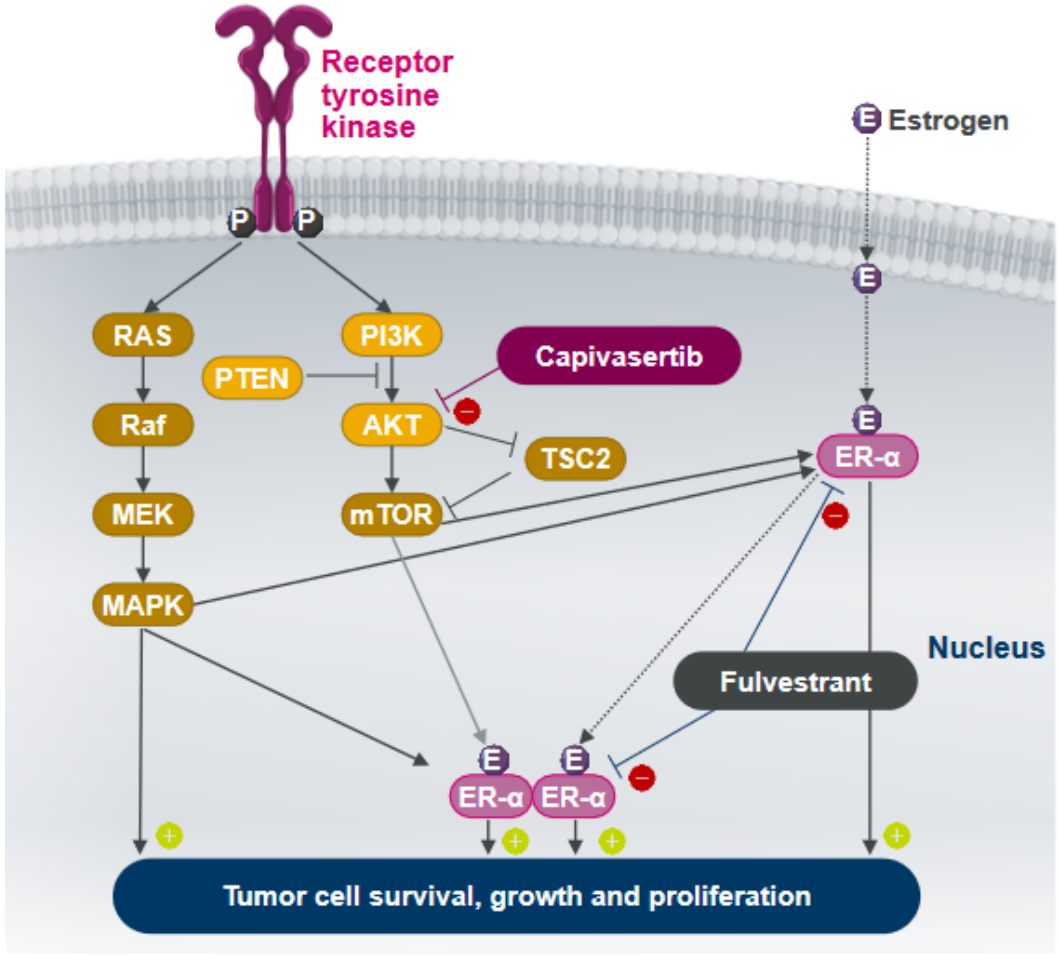
Phase III Capitello-292: AKT inhibitor capivasertib

PI3K-AKT-mTOR pathway alterations are common in HR+ disease

- PIK3CA-mt 30-40%
- PTEN loss is mechanism for resistance to PI3K inhibitors

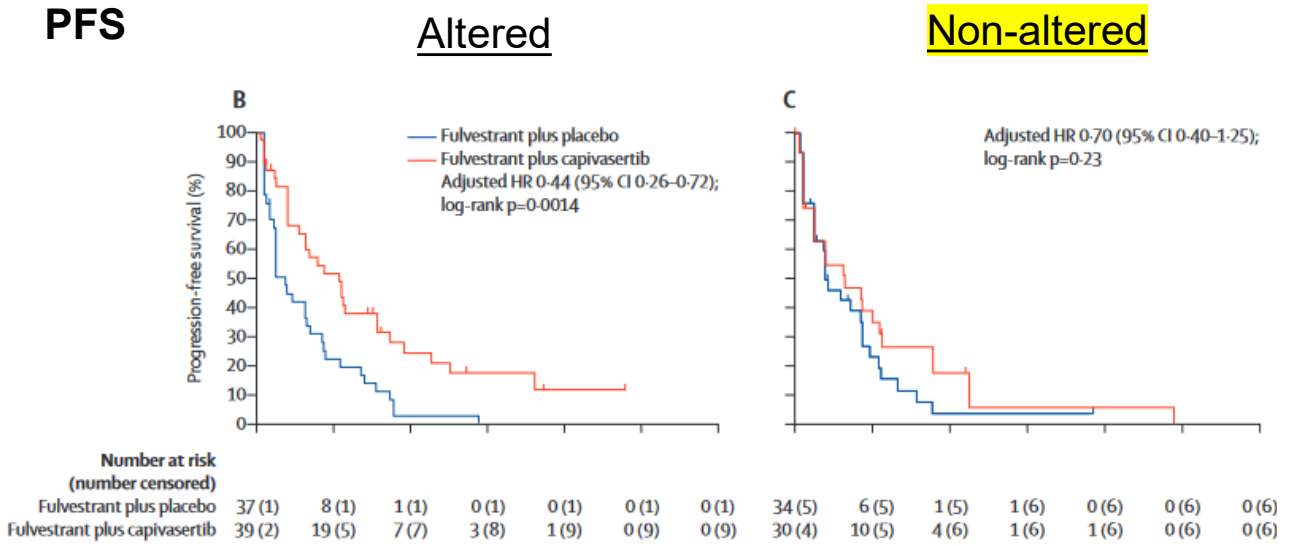
Capivasertib AKT1/2/3 inhibitor

- AKT mutant isoforms are weak oncogenes
- AKT1 E17K hotspot is found in 3% HR+ breast
- AKT2/3 can be amplified but rarely mutated

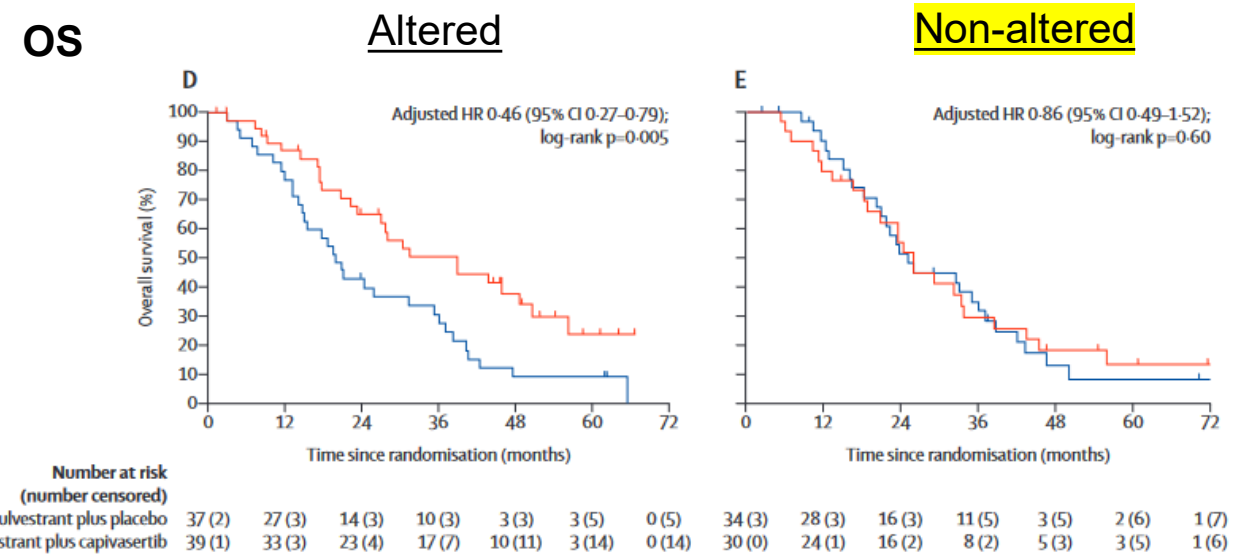


P2 FAKTION: Capivasertib + Fulvestrant
PFS/OS by PIK3CA, AKT-mt or PTEN loss

PFS



OS



P3 CAPItello-292: fulvestrant +/- capivasertib

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence 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)

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

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

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

P3 CAPItello-292: fulvestrant +/- capivasertib

AKT pathway alterations

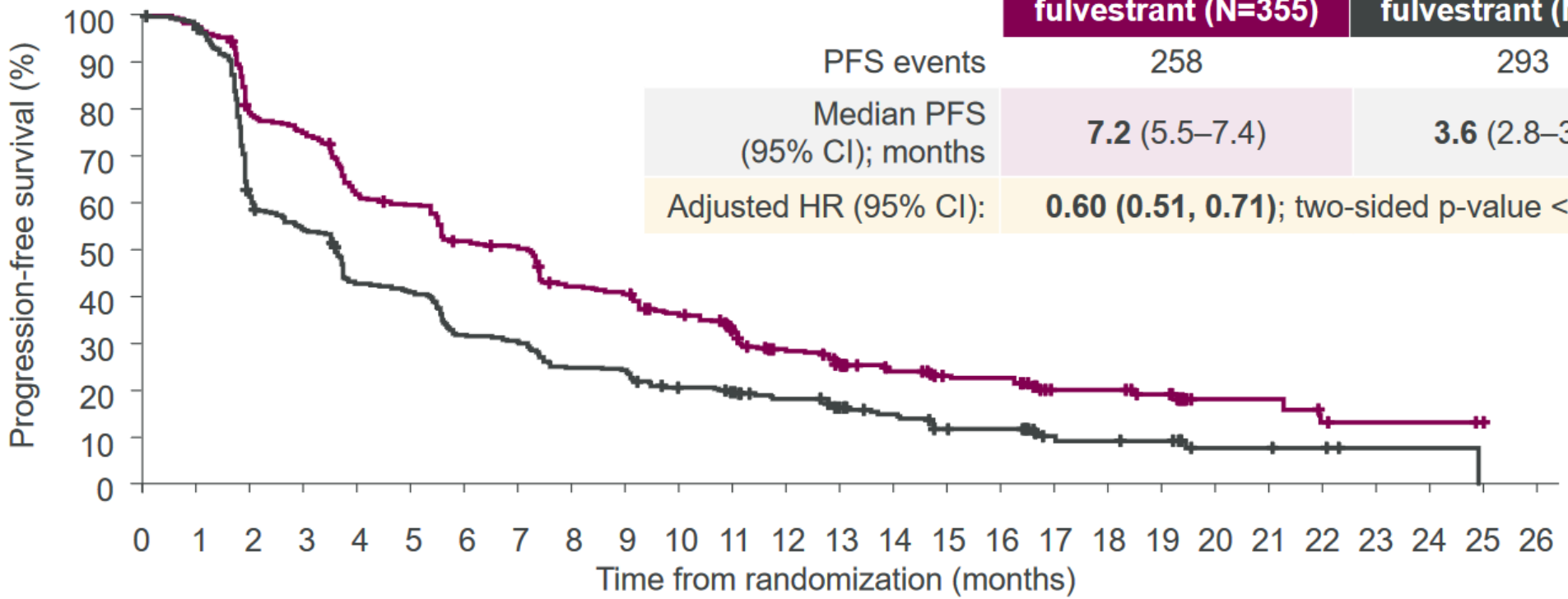
Alteration; n (%)		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
Any AKT pathway alteration		**155 (43.7)**	**134 (38.0)**
PIK3CA	Any	116 (32.7)	103 (29.2)
	PIK3CA only	110 (31.0)	92 (26.1)
	PIK3CA and *AKT1*	2 (0.6)	2 (0.6)
	PIK3CA and *PTEN*	4 (1.1)	9 (2.5)
AKT1 only		18 (5.1)	15 (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)

P3 CAPItello-292: fulvestrant +/- capivasertib

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

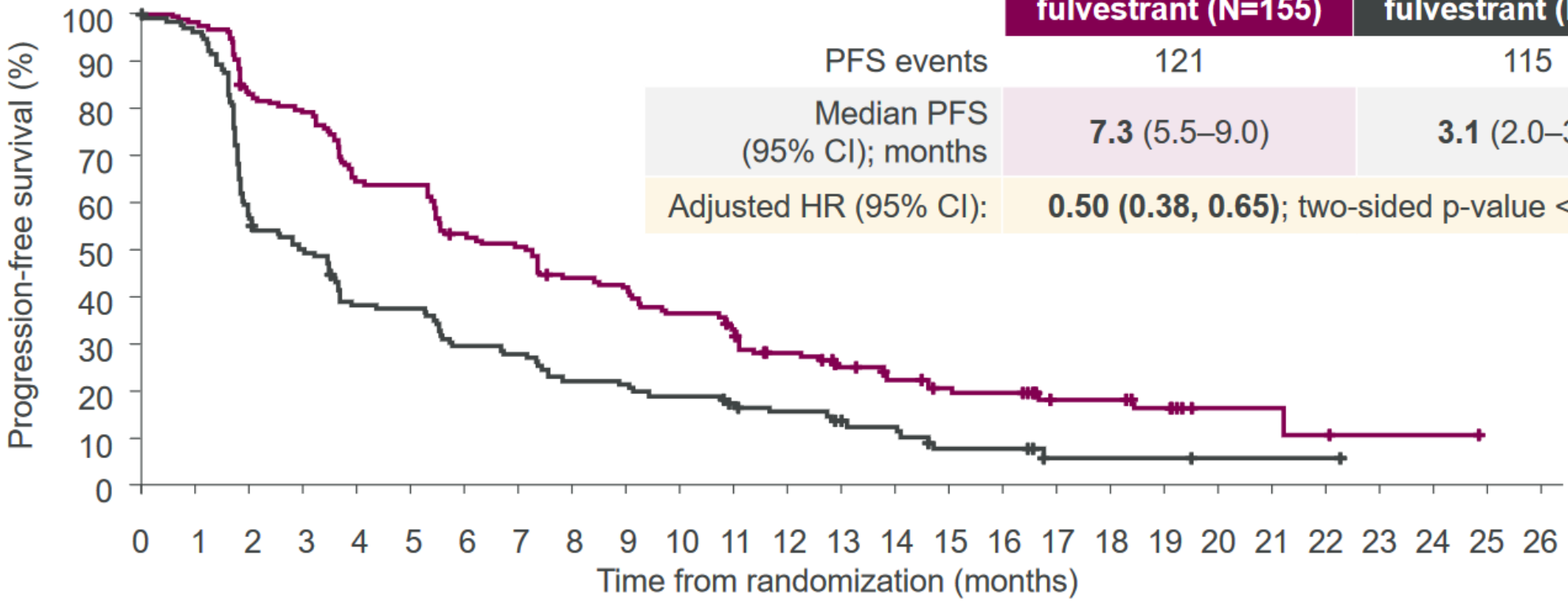
Capivasertib + fulvestrant	355	330	266	252	207	199	172	166	138	133	115	98	78	64	55	44	43	25	25	21	8	8	5	2	2	1	0
Placebo + fulvestrant	353	329	207	182	142	136	106	100	83	81	66	59	51	41	33	24	23	12	11	10	4	4	3	1	1	0	0

+ 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.

P3 CAPItello-292: fulvestrant +/- capivasertib

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

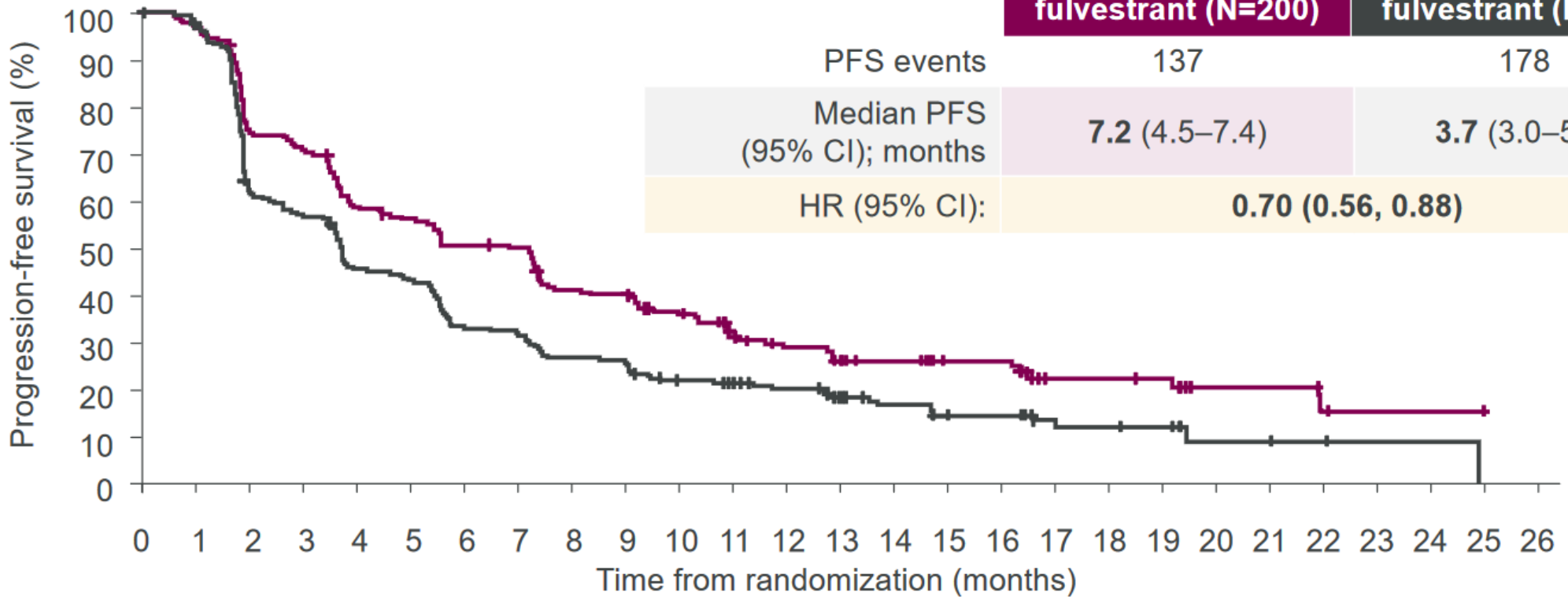
Capivasertib + fulvestrant	155	150	127	121	99	97	80	76	65	62	54	49	38	31	26	22	21	12	12	9	3	3	2	1	1	0	0
Placebo + fulvestrant	134	124	77	64	48	47	37	35	28	27	24	20	17	14	11	6	6	2	2	2	1	1	1	0	0	0	0

P3 CAPItello-292: fulvestrant +/- capivasertib

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

16% (capi arm) and 13% (placebo arm)

	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

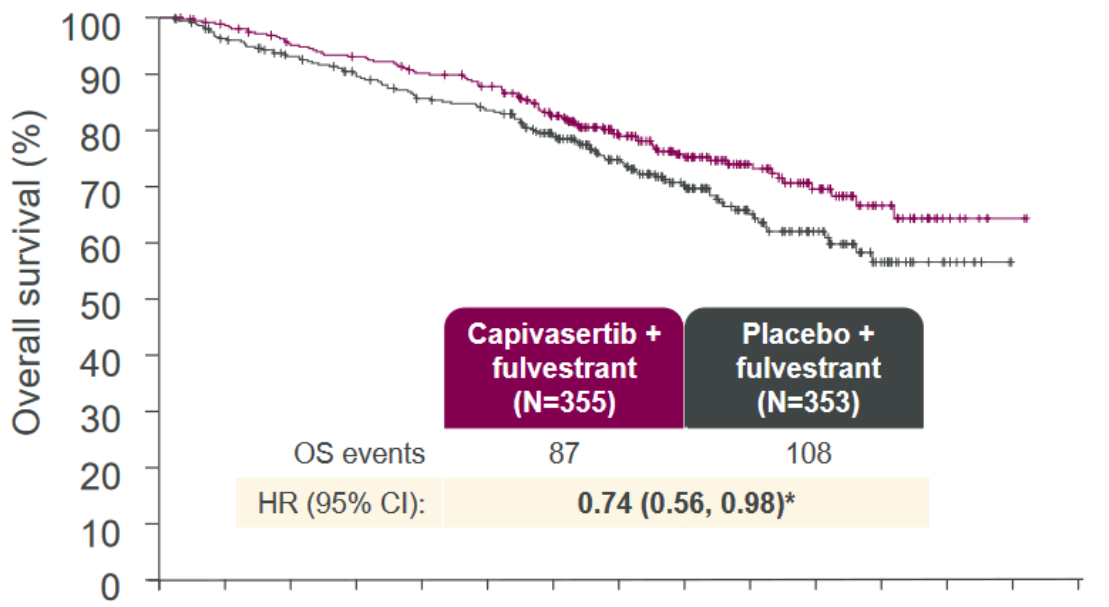
+ indicates a censored observation. †Patients with no valid NGS results. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and prior use of CDK4/6 inhibitor.

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

P3 CAPItello-292: fulvestrant +/- capivasertib

Overall survival at 28% maturity overall

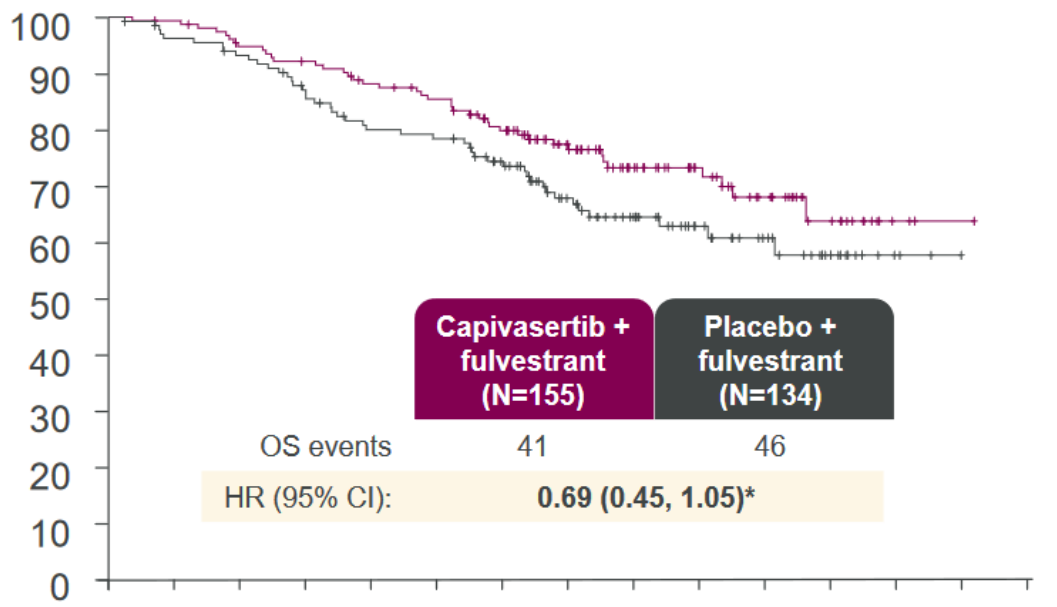
Overall population



Number of patients at risk

Capivasertib + fulvestrant	355	343	327	318	306	295	258	198	144	95	63	33	9	2	0
Placebo + fulvestrant	353	334	316	301	283	274	237	181	134	90	59	30	11	0	0

AKT pathway-altered population

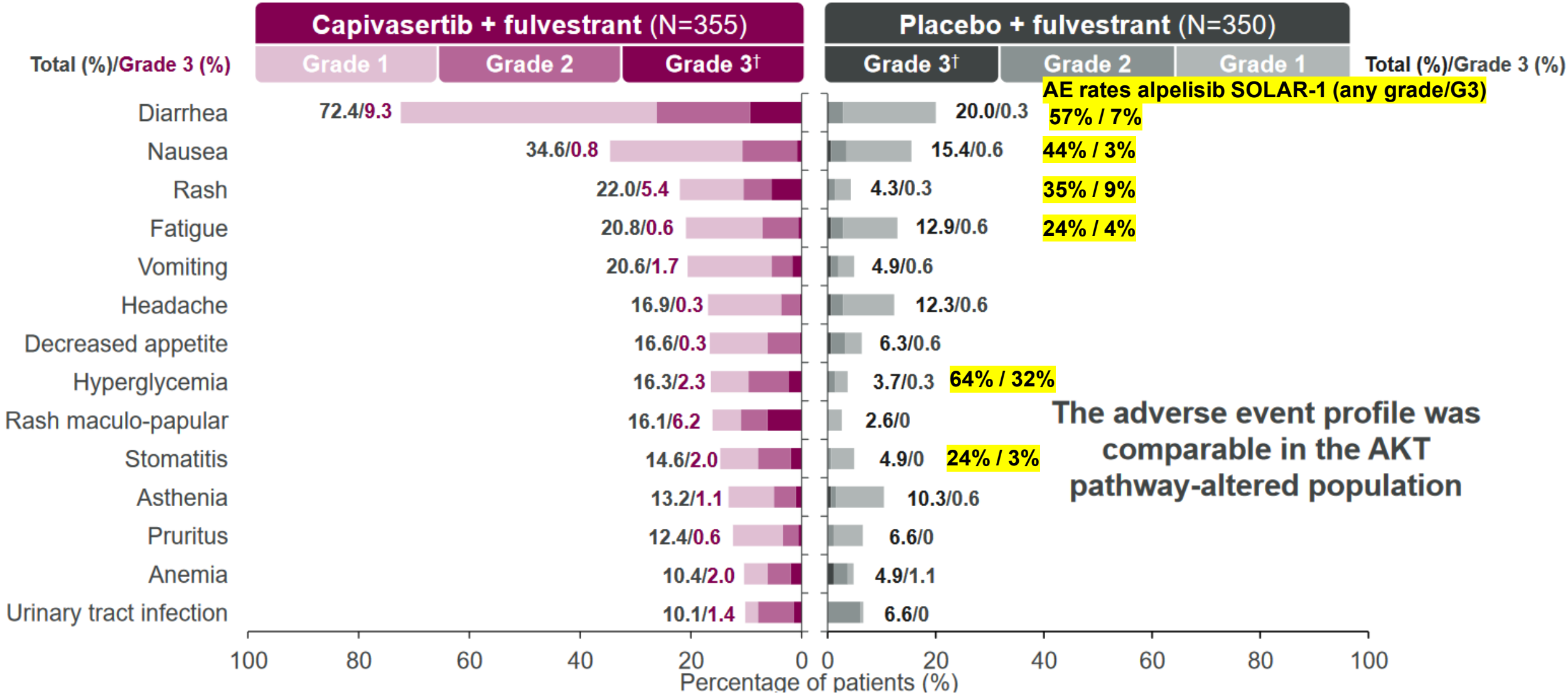


Capivasertib + fulvestrant	155	153	144	139	131	125	111	83	60	45	30	14	3	1	0
Placebo + fulvestrant	134	127	122	112	101	99	87	62	46	31	22	13	3	0	0

*0.01% alpha penalty assigned to OS analyses of no detriment. Formal analysis not prespecified. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases (overall population only) and prior use of CDK4/6 inhibitor.

P3 CAPItello-292: fulvestrant +/- capivasertib

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



AE rates alpelisib SOLAR-1 (any grade/G3)

57% / 7%

44% / 3%

35% / 9%

24% / 4%

64% / 32%

24% / 3%

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

Capivasertib summary

- Combination capivasertib + fulvestrant
  - Improvement in PFS (7.2 versus 3.6m)
  - Likely OS benefit

- Performed equally well in PIK3CA, AKT, PTEN alterations disease

- Benefit consistent across clinically relevant subgroups
  - Prior CDK, liver metastases

- Safety – side effects similar to alpelisib & everolimus - diarrhea, N/V, stomatitis, hyperglycemia

- Dosing schedule maybe challenging (BID 4d on 3d off)
- Potential interaction with metformin and capivasertib (?metformin given days capivasertib is administered)

- Capivasertib, alpelisib, or everolimus? (SOLAR-1; BOLERO-2, TAMRAD, GINECO)

Capivasertib upcoming trials

- CAPItello-292: capivasertib, palbociclib, fulvestrant for HR+HER2- advanced breast cancer

- Fulvestrant +/- capivasertib advanced HR+HER2-

- T-DXd + capivasertib (HER2-low, P1 Destiny Breast 08)
  - At least 1 prior line of therapy (ET acceptable for HR+ disease)
  - DB08 also includes durvalumab, paclitaxel, anastrozole, fulvestrant, capecitabine

- <u>For TNBC:</u>
- Capivasertib + paclitaxel for 1L mTNBC

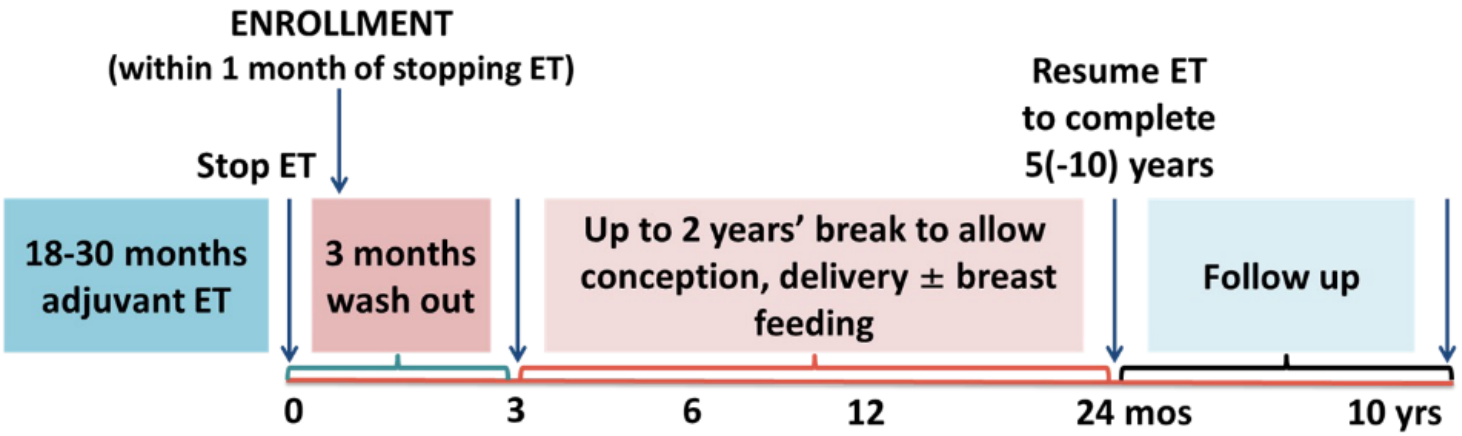
- AMTEC (OHSU): Olaparib + capivasertib in mTNBC
  - PI3K pathway alterations by NGS and NanoString DSP (p-AKT, PRAS40, GSK3B), PTEN loss by IHC

POSITIVE: Safety of interrupting therapy for pregnancy

Interruption of ET to attempt pregnancy has not been prospectively studied

Eligibility

- Stage I-III HR+ breast cancer
- Age <43
- Prior chemo and fertility preservation allowed



Endpoints:

- BCFI after 18-30m
- Pregnancy/offspring outcomes
- Breast feeding
- Assisted reproductive technology
- Adherence to endocrine treatment
- SOFT/TEXT external control

If no pregnancy by 1y, fertility assessment strongly recommended
ET resumption strongly recommended after pregnancy to complete 5-10y

Retrospective analysis

What about timing?

- Mueller et al., (2003)
  - <3 months RR 1.7 (95% CI: 1.2 – 2.6)
  - 4-6 months RR 1.0 (95% CI: 0.55 – 1.9)
  - 7-9 months RR 0.38 (95% CI: 0.12 – 1.2)
  - 10-12 months RR 1.0 (95% CI: 0.23 – 4.8)
  - 2-3 years RR 0.49 (95% CI: 0.27 – 0.86)
  - 3-4 years RR 0.30 (95% CI: 0.12 – 0.71)
  - 4-5 years RR 0.19 (95% CI: 0.05 – 0.81)

- Azim et al. meta analysis:
  after 2 years, overall mortality: RR 0.55 (95% CI: 0.36 – 0.84)

- Verkooijen et al.
  - risk of death decreases the further from diagnosis of breast cancer; within 1-2 years 3-fold higher relative mortality vs. 4 years

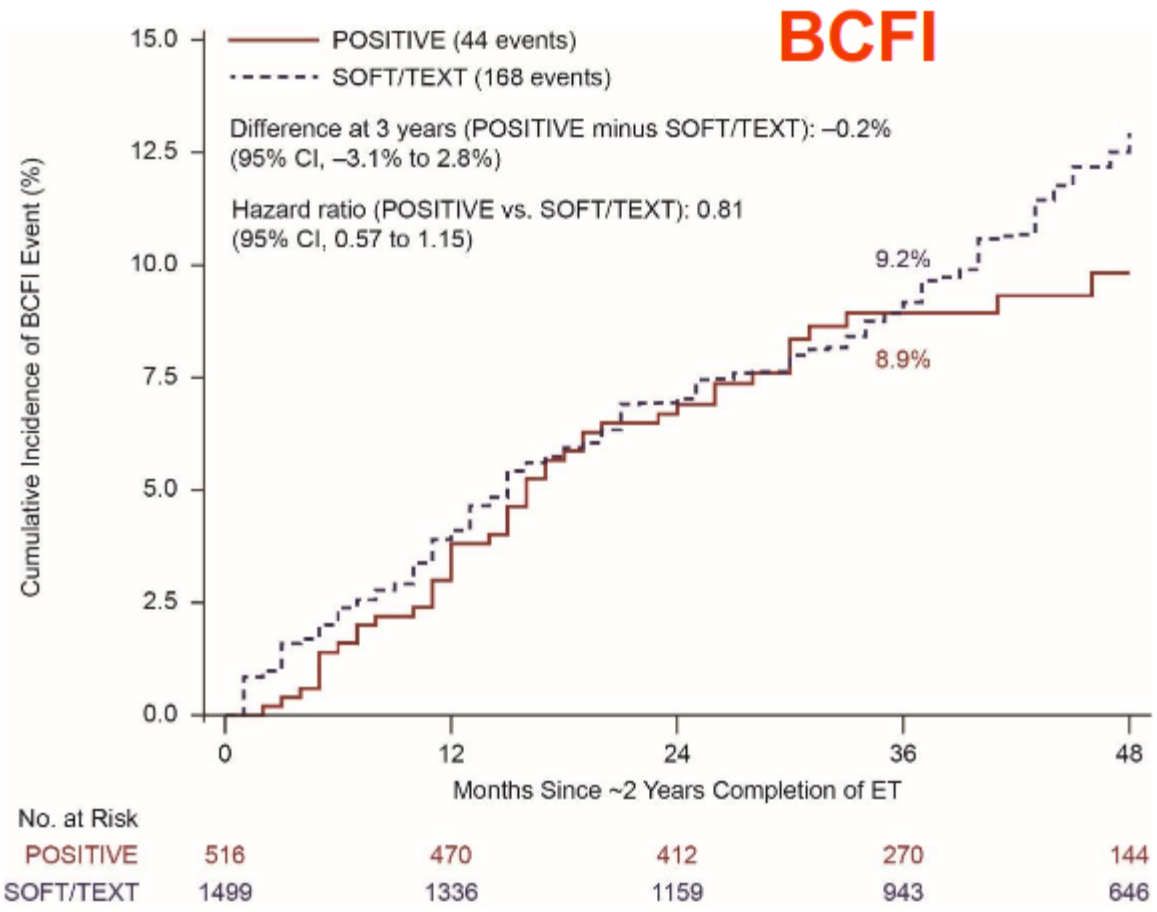
Mueller BA et al., Cancer 2003 98(6):1131; Azim HA Jr et al., Eur J Cancer 2011 47(1):74; Verkooijen HM et al., Br J Surg 2010 97(8):1253

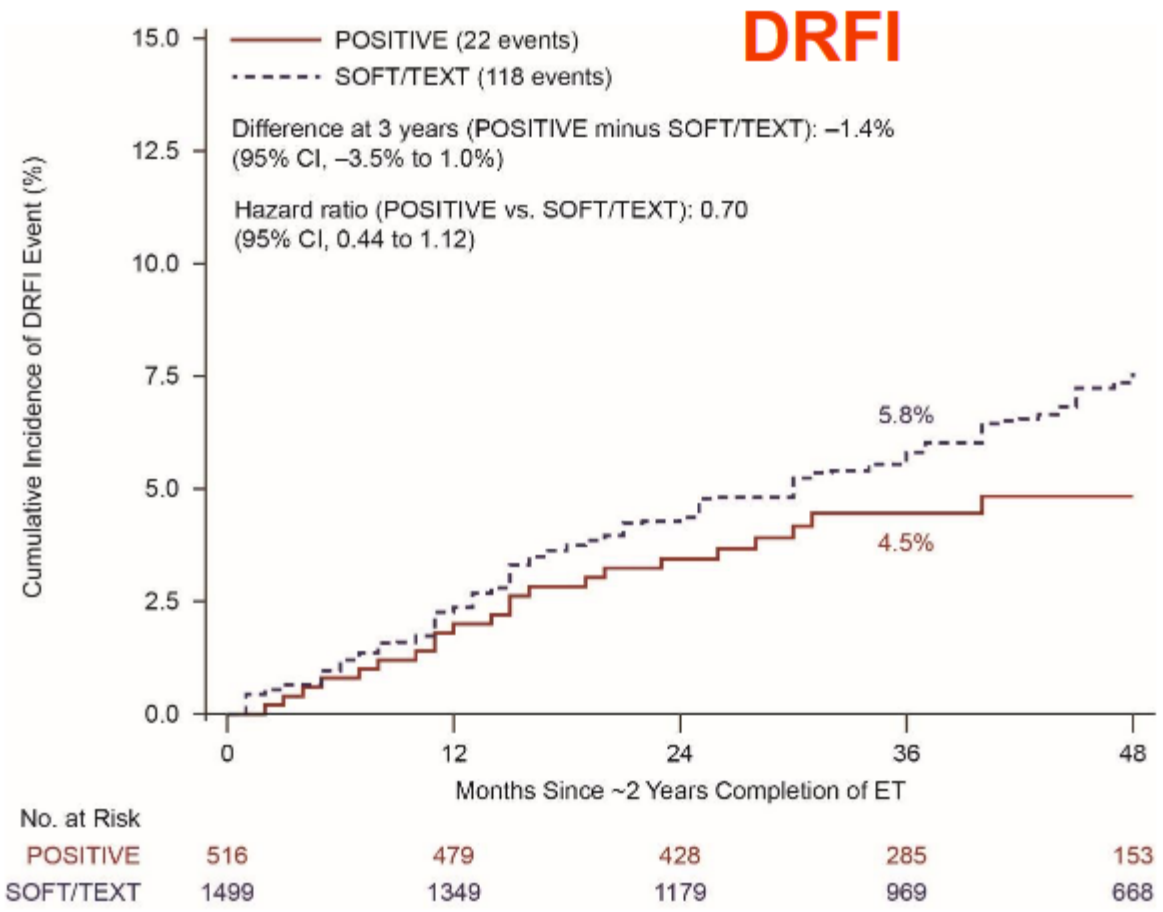
POSITIVE: Safety of interrupting therapy for pregnancy

	N	%
	516	**100**
Age at enrollment *Median 37 years (range 27-43 years)*		
<35	177	34%
35-39	221	**43%**
40-42	118	23%
Number of prior births		
0	387	**75%**
1	107	21%
≥ 2	22	4%
TNM stage		
I	242	**47%**
II	240	**47%**
III	31	6%
Unknown	3	1%

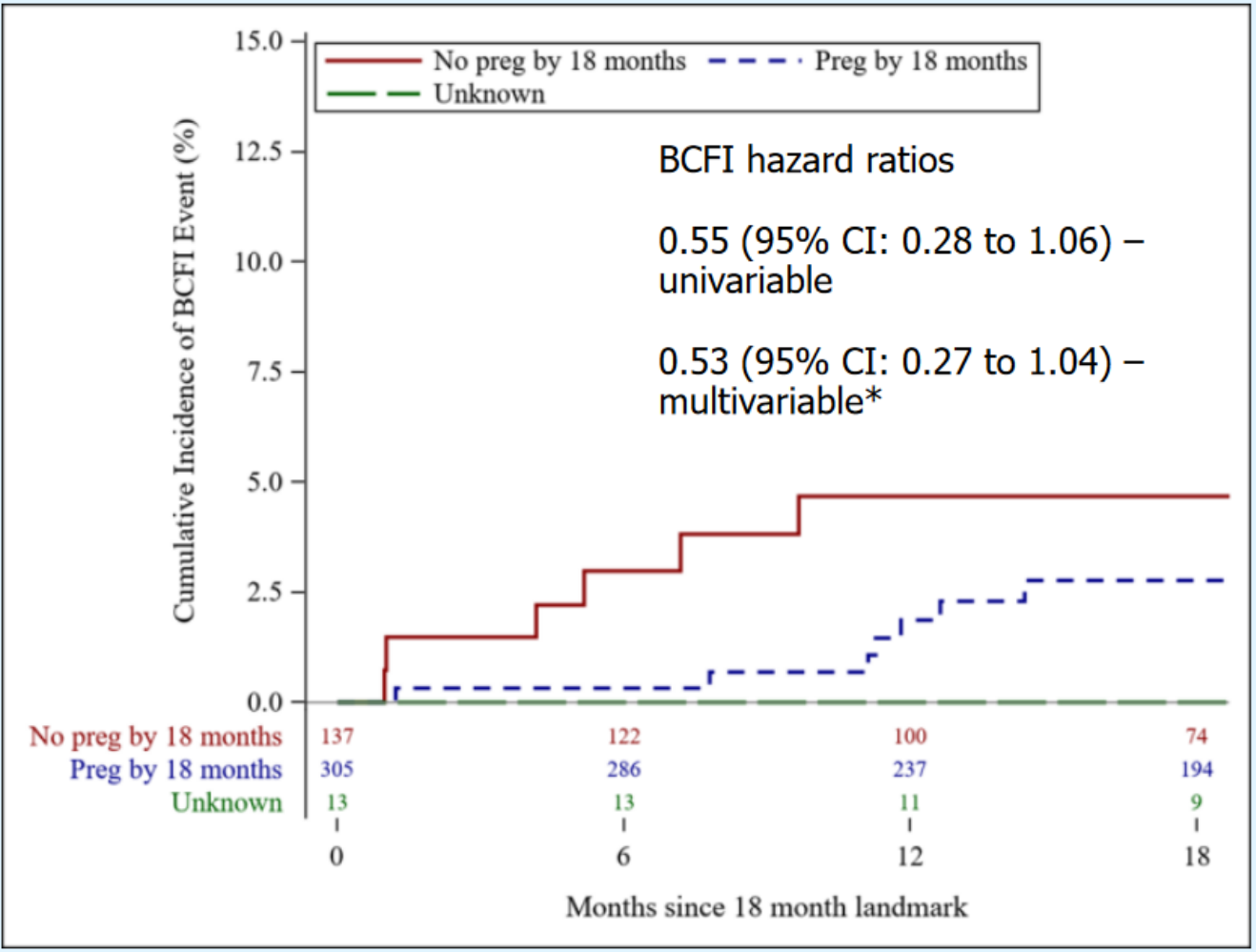
	N	%
	516	**100**
Endocrine therapy prior to enrollment *Median duration: 23.4 months*		
SERM alone	215	**42%**
SERM+OFS	184	**36%**
AI+OFS	82	16%
Other	35	7%
Prior (neo-)adjuvant chemotherapy		
None	196	38%
Yes	320	**62%**
Breast surgery		
Mastectomy	233	45%
Breast conserving procedure	283	55%

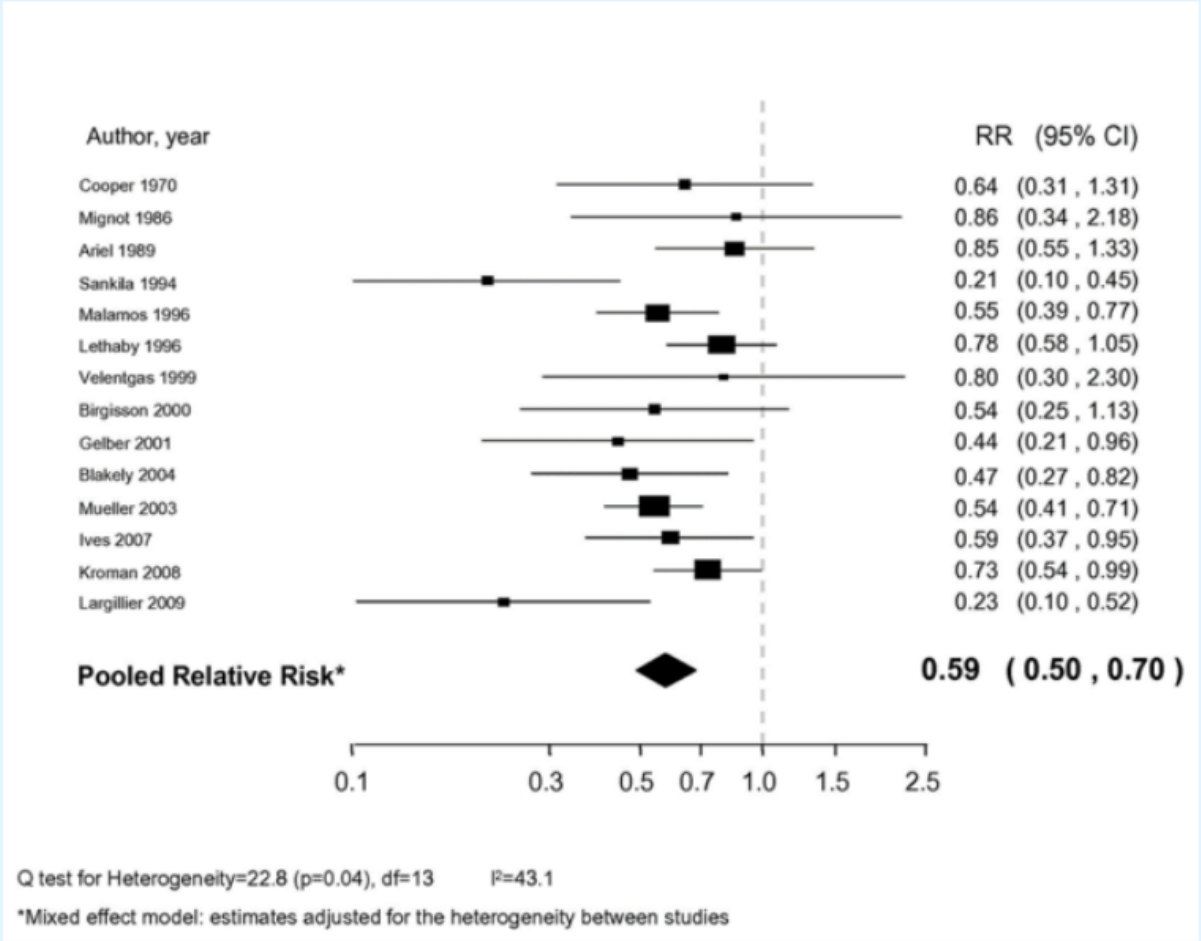
POSITIVE: Safety of interrupting therapy for pregnancy





POSITIVE: Outcomes by pregnancy vs no pregnancy





Azim HA Jr et al., Eur J Cancer 2011 47(1):74

Meta-analysis of 14 studies
(1244 cases, 18k controls)
Pregnant after BC ddx 41% reduced risk of death

POSITIVE: Safety of interrupting therapy for pregnancy

- 368 (74%) of the 497 women in the secondary endpoint population had at least one pregnancy (70% within 2 years) for a total of 507 pregnancies
- 317 had at least one live birth (64% of all women, 86% of those who became pregnant)

	N	% of 497	% of 368
Secondary endpoint population	497	100%	
At least one on trial pregnancy	368	**74%**	100%
At least one live birth (full-term or preterm)	317	**64%**	**86%**
At least one miscarriage	93	19%	25%
At least one elective abortion	16	3%	4%
At least one stillbirth/neonatal death	1/1	0.2% / 0.2%	0.3% / 0.3%

Note: 110 women had more than one pregnancy, and may contribute information to more than one row

- **Delivery**
  - Vaginal 66%
  - Cesarean section 34%
- **Pregnancy complications**
  - 11% of pregnancies
  - Most common:
    Hypertension/preeclampsia 3%
    Diabetes 2%

No significant differences in offspring outcomes compared to general population (2% birth defects, not associated to treatment exposure)

POSITIVE: Summary and general practice recommendations

- HR-
  - Wait 18+ months
- HR+
  - Endocrine therapy x18-30m
  - Consider OFS+AI prior to fertility attempt
  - Tamoxifen washout 3-6m

Questions?