RAGMA 23

16ª Revisión Anual GEICAM de Avances en Cáncer de Mama

Realidades y esperanzas

Enfermedad con expresión de receptores hormonales

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Hospital Universitario de Navarra

Organizado por:

GEICAM investigación en cáncer de mama

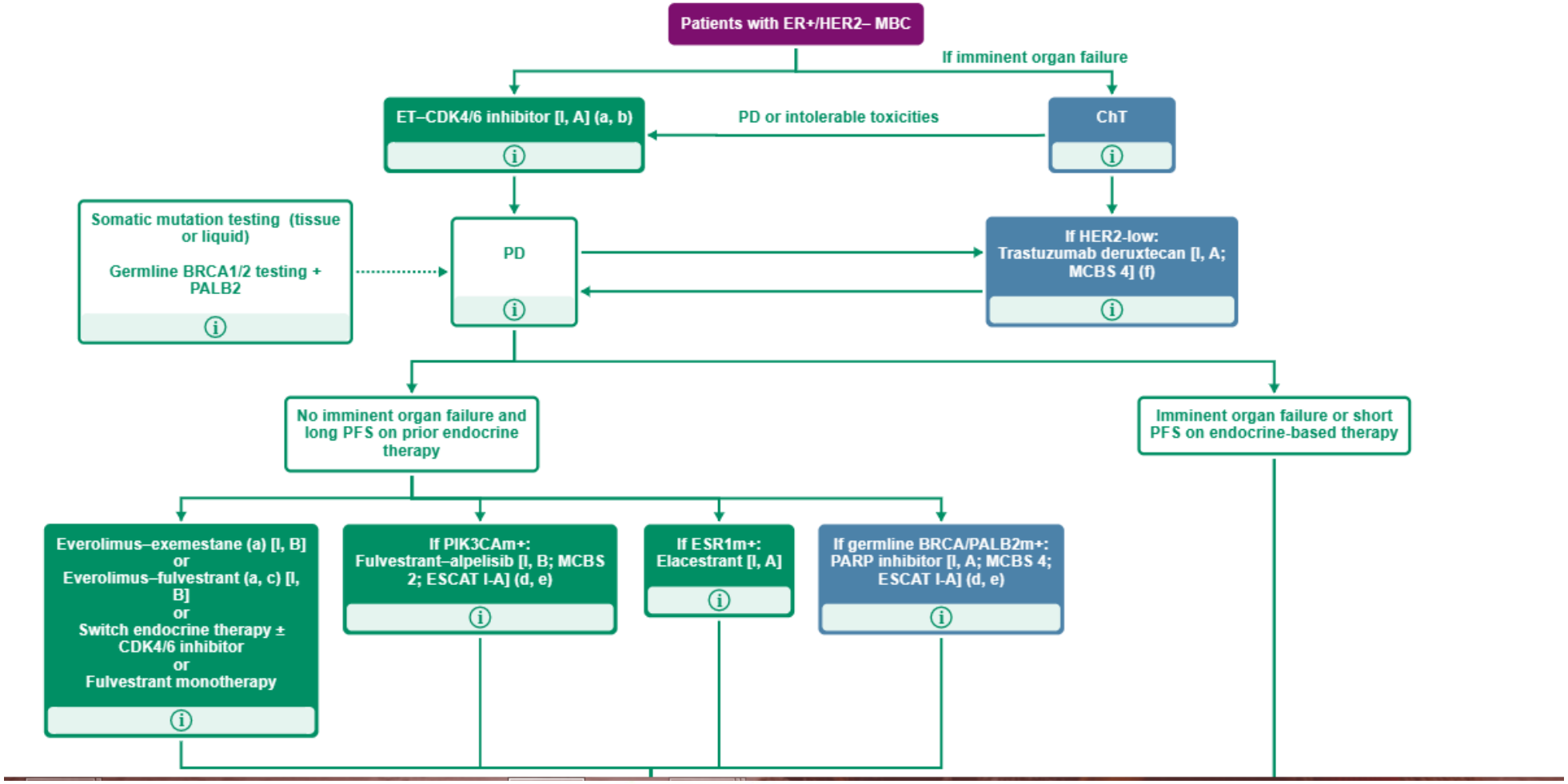
Disclosurers

- Employment: Servicio Navarro de Salud.
- Advisory role: Pfizer, alianza AstraZeneca-Daichi Sankyo, Seagen, Adamed.
- Travel grant: Novartis, Pfizer.

Outline

- Introduction.
- First line: CDK4/6i vs chemotherapy → RIGHT choice.
- Progression to CDK4/6i:
  - Re-challenge with CDK4/6i → PACE, MAINTAIN.
  - Change endocrinal therapy and keep CDK4/6i → PALMIRA.
  - Early "switch" by ctDNA ESR1→ PADA-1.
  - Endocrine treatment +Targets: ESR1, PIK3CA, AKT → EMERALD, SERENA-2, CAPITELLO
  - Chemotherapy → TROPiCS-02, X-7/7.
- CDK4/6i for everyone on the front line??.

ER POSITIVE METASTATIC BREAST CANCER: Treatment algorythm



ESMO MBC Guidelines, v1.1 May 2023

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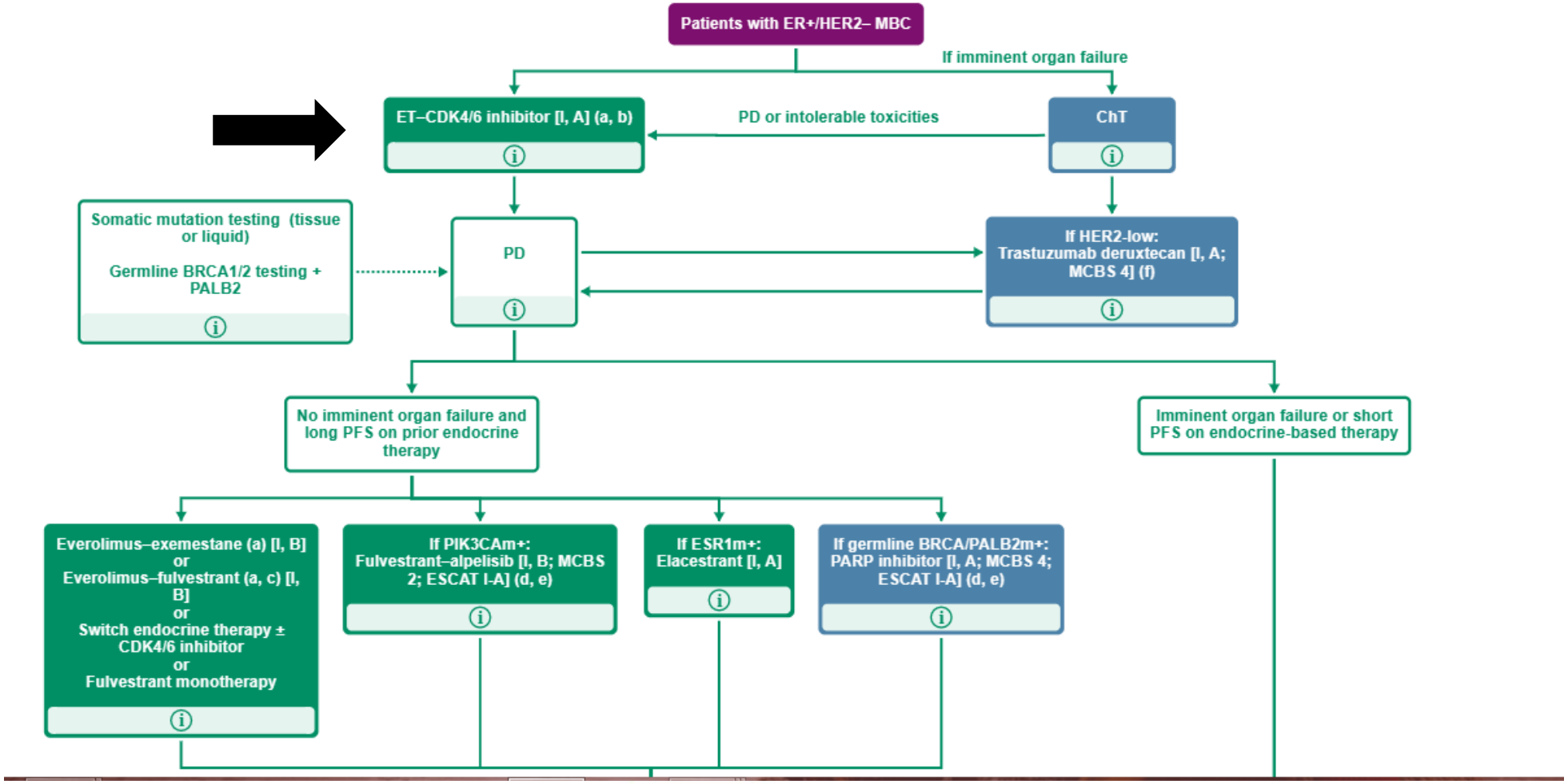

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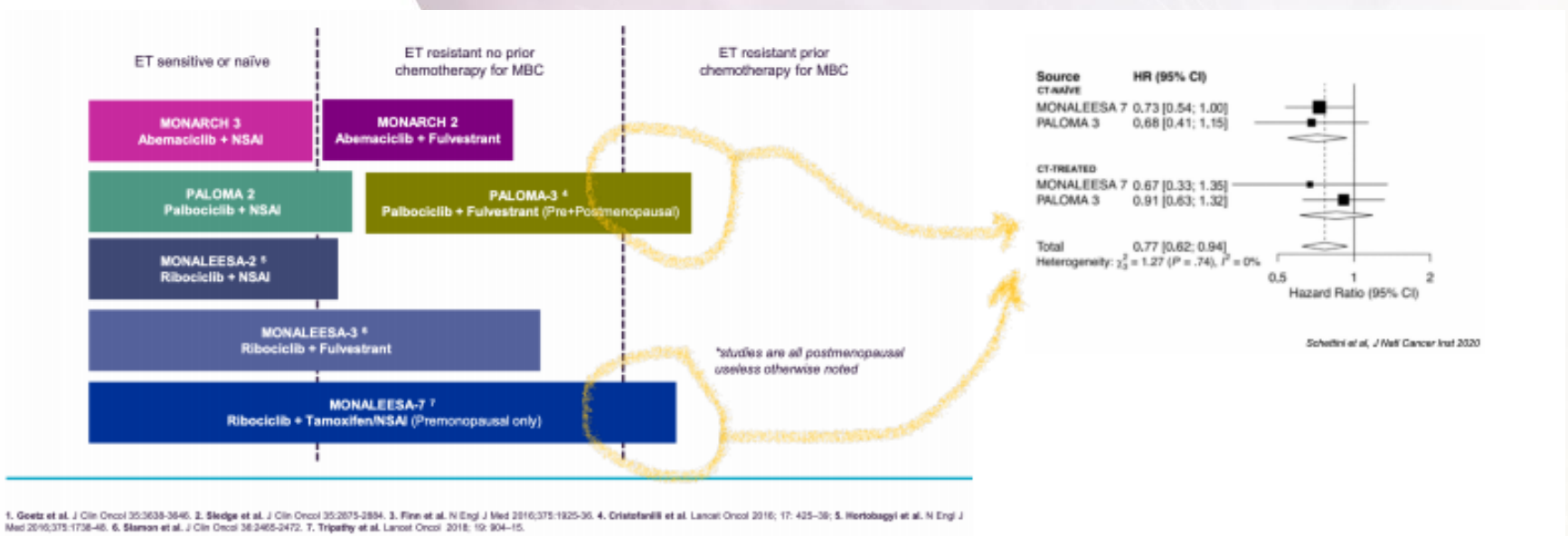
The advantage of CDK 4/6 inhibitors: Trials overview



1. Goetz et al. J Clin Oncol 35:3638-3646. 2. Sledge et al. J Clin Oncol 35:2875-2884. 3. Finn et al. N Engl J Med 2016;375:1925-36. 4. Cristofanilli et al. Lancet Oncol 2016; 17: 425–39; 5. Hortobagyi et al. N Engl J Med 2016;375:1738-48. 6. Slamon et al. J Clin Oncol 36:2465-2472. 7. Tripathy et al. Lancet Oncol 2018; 19: 904–15.

	PALOMA 1	PALOMA 2	PALOMA 3	MONALEESA 2	MONALEESA 7	MONALEESA 3	MONARCH 3	MONARCH 2	MONARCH Plus
Phase	II	III	III	III	III	III	III	III	III
No. of pts	165	666	521	668	672	726	493	669	463
Random	Palbo + letro vs letro	Palbo + letro vs letro	Palbo + F vs F	Ribo + letro vs letro	Ribo + tam/AI vs tam/AI + GnRHa	Ribo + F vs F	Abema + AI vs AI	Abema + F vs F	Abema + AI/F vs AI/F
Setting	1st line	1st line	≥1st line	1st line	1st line	≥1st line	1st line	≥1st line	≥1st line
PFS HR (95% CI)	0.49 (0.32-0.75)	0.58 (0.46-0.72)	0.46 (0.36-0.59)	0.57 (0.46- 0.70)	0.55 (0.44-0.69)	0.59 (0.48-0.73)	0.54 (0.41-0.69)	0.53 (0.44-0.64)	0.50 (0.35-0.72) 0.38 (0.24-0.59)
OS HR (95% CI)	0.81 (0.49-1.35)	NM	0.81 (0.65- 0.99)	0.76 (0.63-0.93)	0.71 (0.54-0.95)	0.72 (0.58-0.89)	NM	0.75 (0.60-0.94)	NM

Progression-free (PFS) and overall survival (OS) data

	PALOMA-2	MONALEESA-2	MONARCH-3
Phase	Phase 3	Phase 3	Phase 3
Line	1st line	1st line	1st line
Endocrine tx	Letrozole	Letrozole	Letrozole or anastrozole
CDK4/i	Palbociclib	Ribociclib	Abemaciclib
Patients (n)	666	668	493
PFS Hazard Ratio	0.58	0.56	0.54
PFS (months)	24.8 vs 14.5	25.3 vs 16	28.2 vs 14.8
OS Hazard Ratio	0.96	0.76	0.75
OS (months)	53.9 vs 51.2	63.9 vs 51.4	67.1 vs 54.5

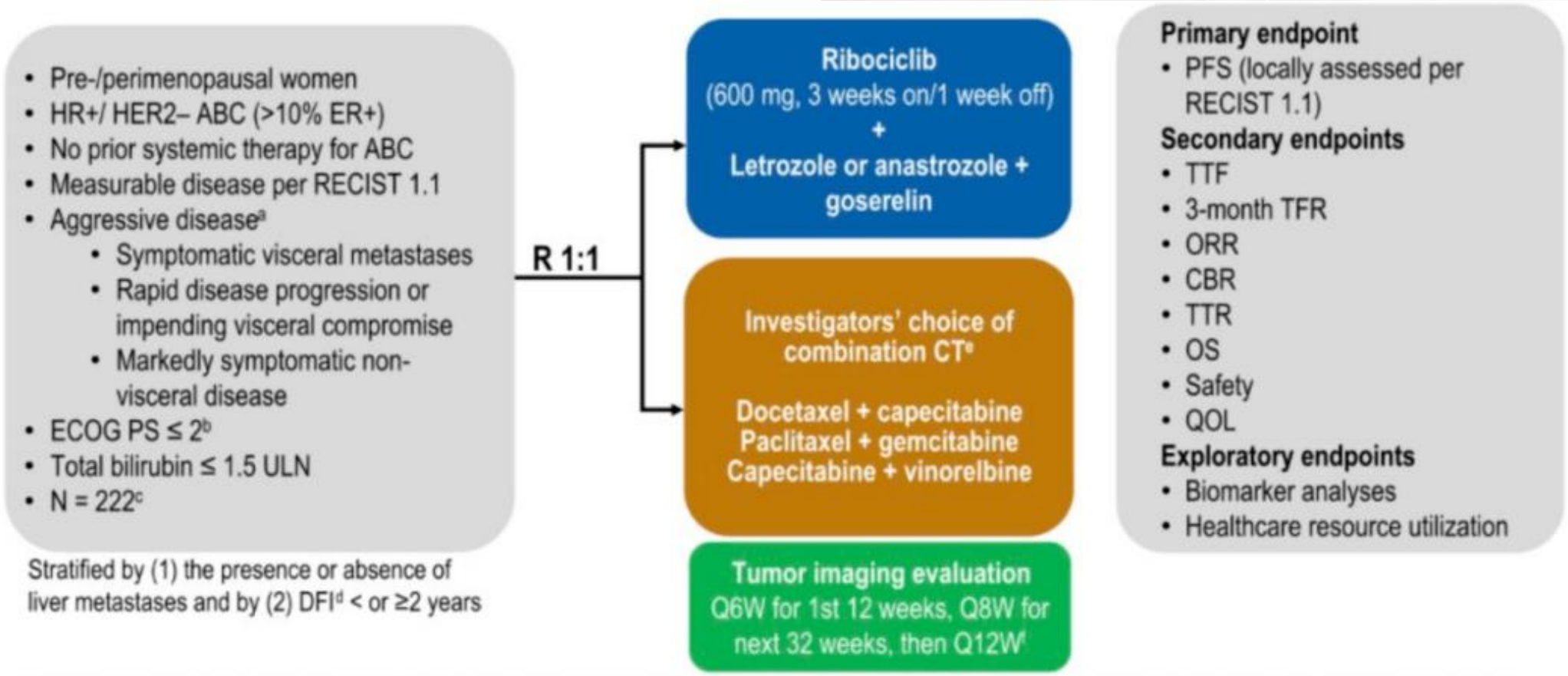
Different studies, different designs, different study populations, different subgroup definitions

Finn NEJM 2016; Hortobagyi NEJM 2016; Goetz J Clin Oncol 2017; Finn, ASCO 2022; Hortobagyi NEJM 2022; Goetz ESMO 2022

CDK 4/6 inhibitors vs chemotherapy

First line in agressive disease: CDK 4/6 inhibitor vs QT

RIGHT Choice study design



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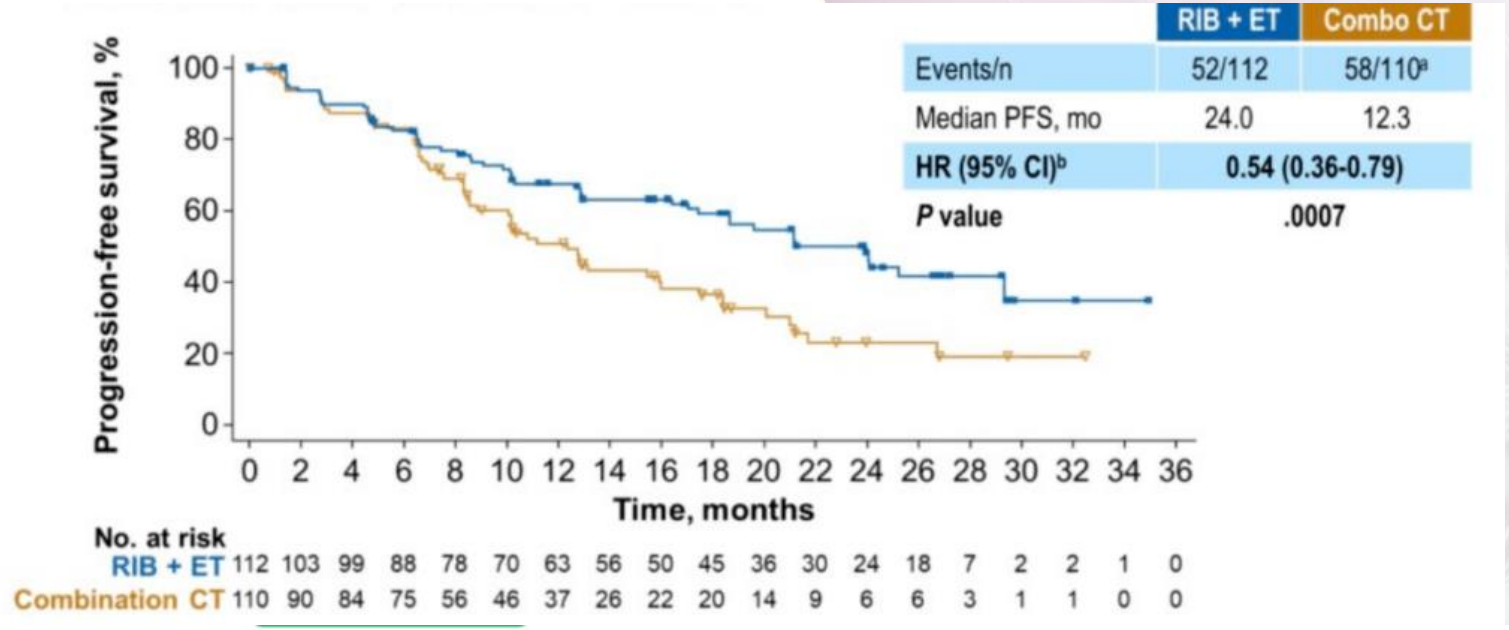
RIGHT Choice results

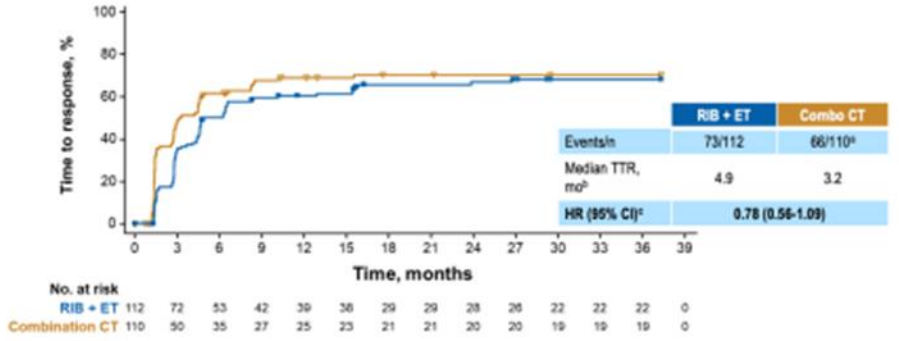
PFS, TTR



	RIB + ET	Combo CT
Events/n	52/112	58/110[a]
Median PFS, mo	24.0	12.3
HR (95% CI)[b]	0.54 (0.36-0.79)	
P value	.0007	

Parameter, n (%)	RIB + ET n = 112	Combo CT n = 110
Disease status		
De novo	71 (63.4)	73 (66.4)
Visceral metastatic sites[a]		
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)

Time to onset of response (TTR)



	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)	

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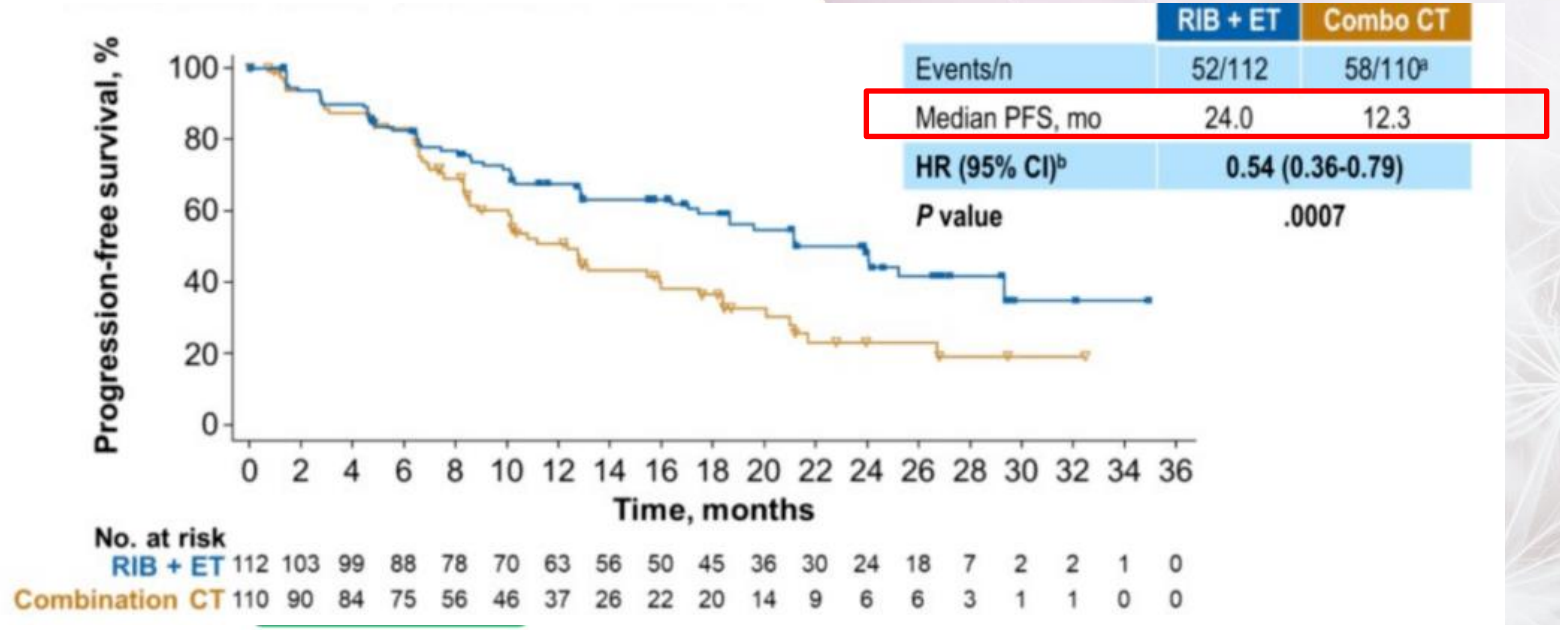

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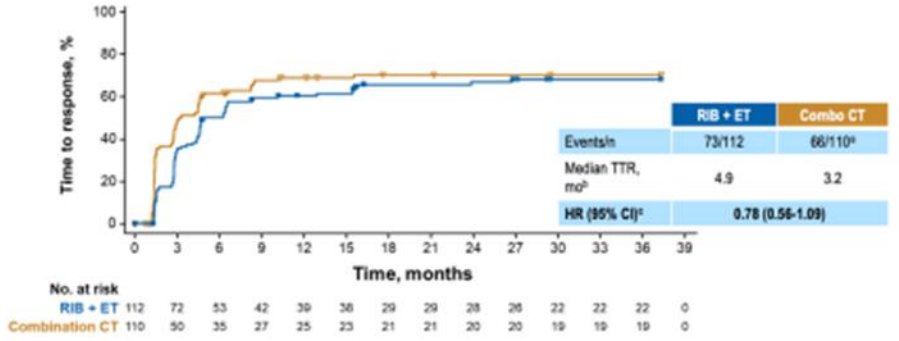

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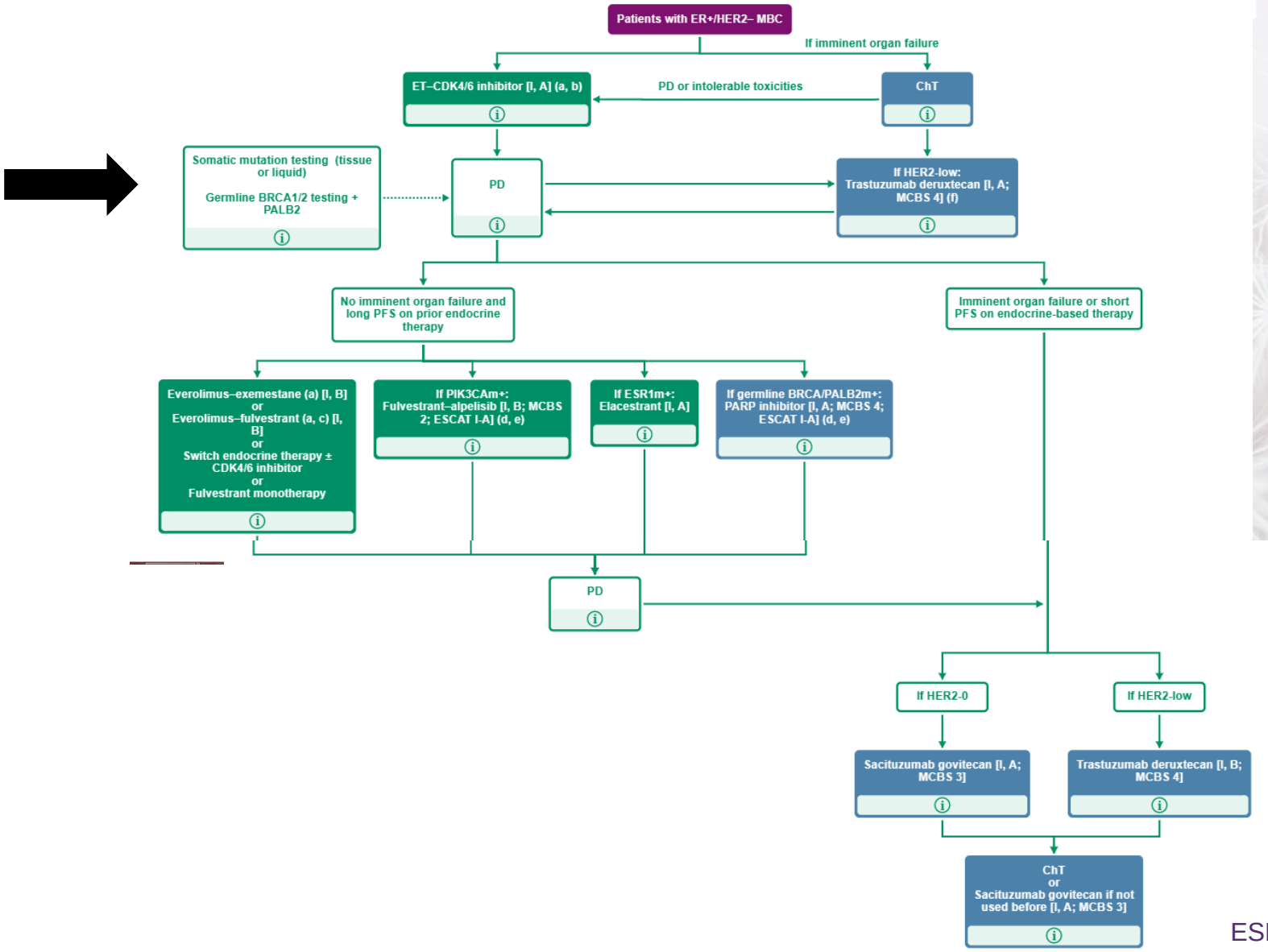
Post CDK 4/6 inhibitors??

ER POSITIVE METASTATIC BREAST CANCER: Treatment algorythm

After CDKi + NSAI



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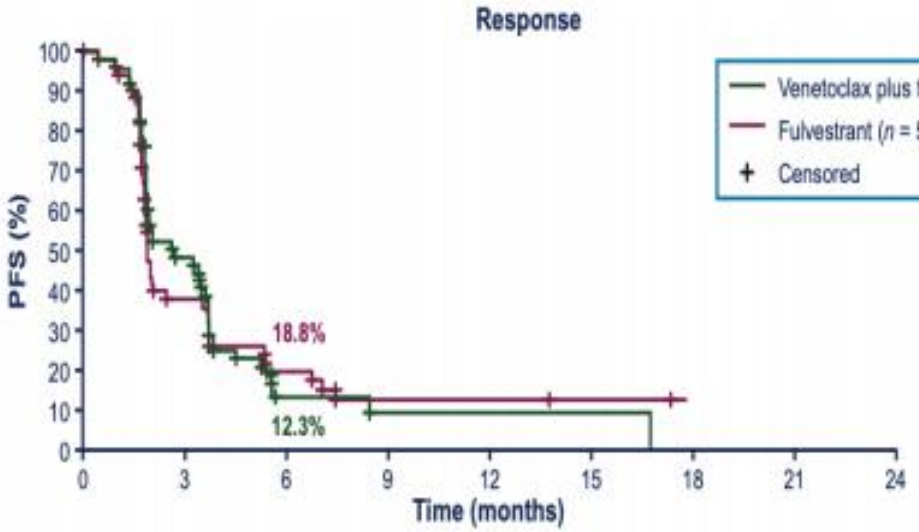
Second line treatment: Fulvestrant

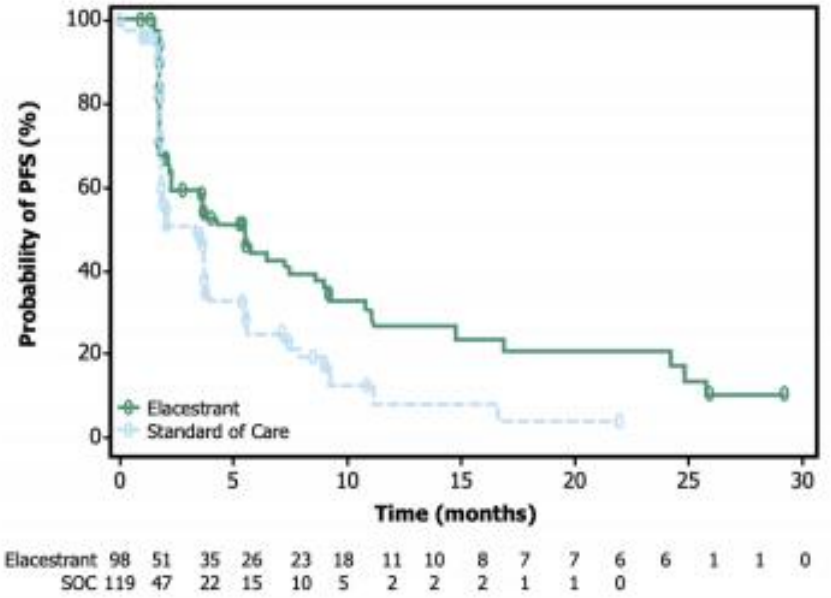


Primary analysis: Aug 5, 2020
Minimum follow-up: 6.0 months
Median follow-up: 9.9 months

No. of patients at risk									
Venetoclax plus fulvestrant									
51	24	3	2	2	2	NE	NE	NE	
Fulvestrant									
52	18	8	4	4	1	NE	NE	NE	

ITT population	Venetoclax plus fulvestrant *n* = 51	Fulvestrant *n* = 52
No. of events, *n* (%)	45 (88.2)	43 (82.7)
Median PFS (months) 95% CI	2.69 1.94–3.71	1.94 1.84–3.55
Stratified HR[c] 95% CI *P*	0.94 0.61–1.45 0.7853	

At least 18 mo CDK4/6i



	0	5	10	15	20	25	30
Elacestrant	98	51	35	26	23	18	11	10	8	7	7	6	6	1	1	0
SOC	119	47	22	15	10	5	2	2	2	1	1	0				

	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)	

Lindeman G. Clin Cancer Res 2022;28:3256-67; Kaklamani V SABCS 2022

Heterogeneity of Luminal Tumors

Implications for therapeutic decisions

Gene or protein	Alteration	Prevalence	ESCAT score
ER	Protein expression ≥ 1% by IHC ESR1 mutation	75% 40%	NA II-A
ERBB2	Amplifications or 3+ (IHC) HER2-low (IHC (1+, 2+ NA)	15%-20% 40%-50%	I-A II-B
	Hotspot mutations	4%	II-B
BRCA1/2	Germline mutations	4%	I-A
	Somatic mutations	3%	II-A
PALB2	Germline mutations	1%	II-A
PD-L1 (TNBC)	Expression by IHC on ICs and tumour cells (CPS)	40%	I-A
PIK3CA (ER+, HER2-)	Hotspot mutations	30%-40%	I-A
MSI	MSI-H	1%-2%	I-C
NTRK	Fusions	<0.1%	I-C
ESR1 (ER+, HER2-)	Mutations (mechanism of resistance)	30%	II-A
AR (TNBC)	AR expression (not validated)	?	II-B
AKT1^{E17K}	Mutations	5%	II-B

2ND LINE POST-CDK4/6i	PFS
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Camizestrant (SERENA-2) – *ESR1*mut	6.3-9.2mo
AI + albelisib (BYLieve) – *PIK3CA*mut	5.7mo
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Can CDK4/6i switch extend endocrine therapy?

MAINTAIN (phase II)

- Multicenter, randomized, placebo-controlled phase II trial

Adults with ER and/or PR ≥1%; HER2- MBC and progression on ET and CDK4/6i; ≤1 CT line for MBC; ECOG PS 0 or 1; postmenopausal (or premenopausal with GnRH agonist); stable brain metastases allowed (N = 120)

→ **Ribociclib** 600 mg QD 3 wk on, 1 wk off **+ Switch ET*** (n = 60)

→ **Placebo + Switch ET*** (n = 59)

*Patients with progression on AI for MBC and no prior fulvestrant received fulvestrant. After protocol amendment, patients who progressed on prior fulvestrant received exemestane.

- **Primary endpoint:** PFS (locally assessed per RECIST v1.1)
- **Key secondary endpoints:** ORR, CBR, safety, tumor response

PACE (phase II)

Obj 1º

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

1:2:1 randomization; stratified by exposure to chemo between CDK4/6i and entry onto trial

N=220

RANDOMIZE

- **Fulvestrant:** 500 mg IM C1D1,15, then q28d
- **Fulvestrant:** 500 mg IM C1D1,15, then q28d **Palbociclib:** 125 mg PO qd 1-21d in a 28d cycle (or lower starting dose to match prior treatment)
- **Fulvestrant:** 500 mg IM C1D1,15, then q28d **Palbociclib:** 125 mg PO qd 1-21d in a 28d cycle (or lower starting dose to match prior treatment) **Avelumab:** 10 mg/kg IV q14d

Baseline archival tissue Baseline ctDNA, CTC | ctDNA | ctDNA, CTC | ctDNA | ctDNA CTC

Primary objective: To compare PFS (RECIST-confirmed) for fulvestrant+palbociclib vs. fulvestrant alone

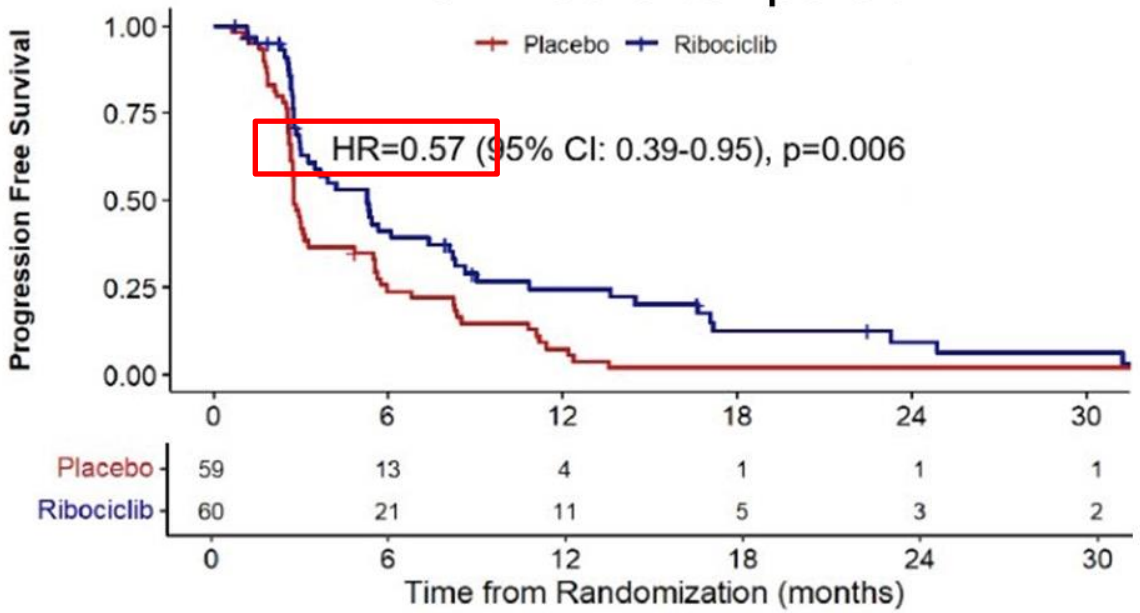
Secondary objectives: To compare PFS for fulvestrant+palbociclib+avelumab vs fulvestrant alone, response endpoints, safety, outcomes in predefined molecular subgroups including ESR1, PIK3CA, and Rb.

Kalinsky ASCO 2022, Kalinsky JCO 2023, Erica L Mayer SABCS 2022

Can CDK4/6i switch extend endocrine therapy?

MAINTAIN

ET +/- “ribo after palbo”

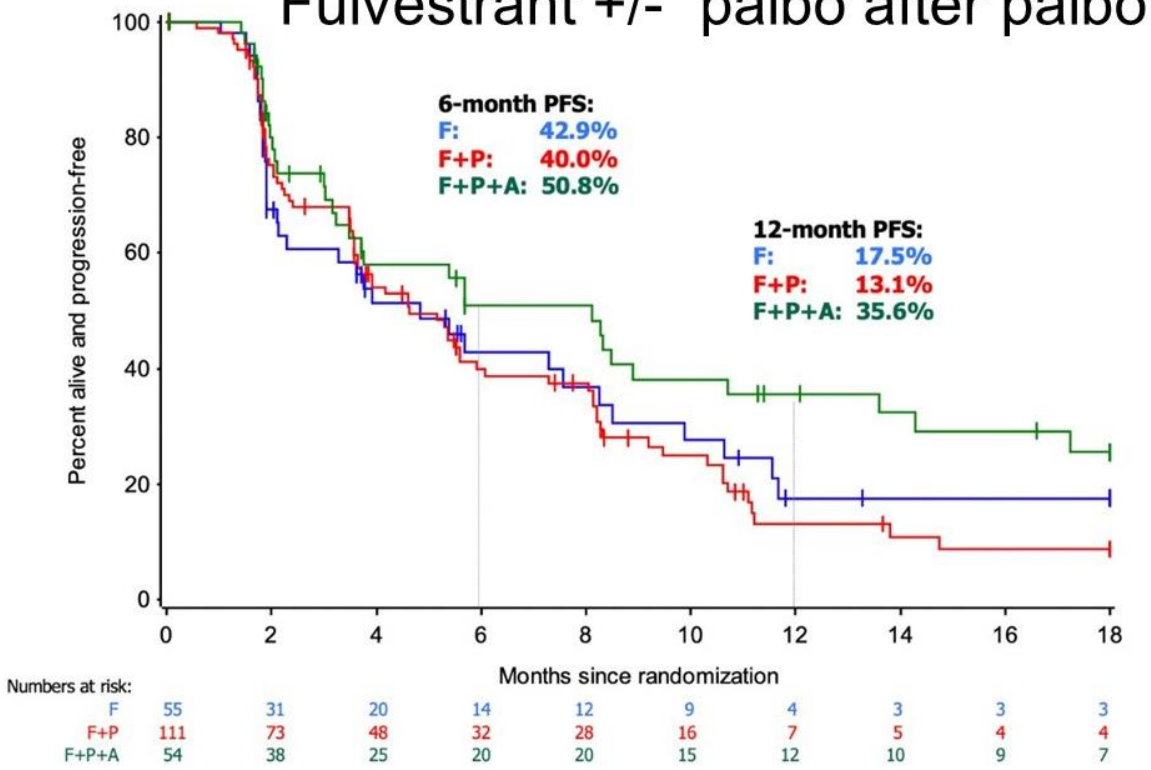


Kalinsky *JCO* 2023

Significant PFS benefit in ribociclib group

PACE

Fulvestrant +/- “palbo after palbo”



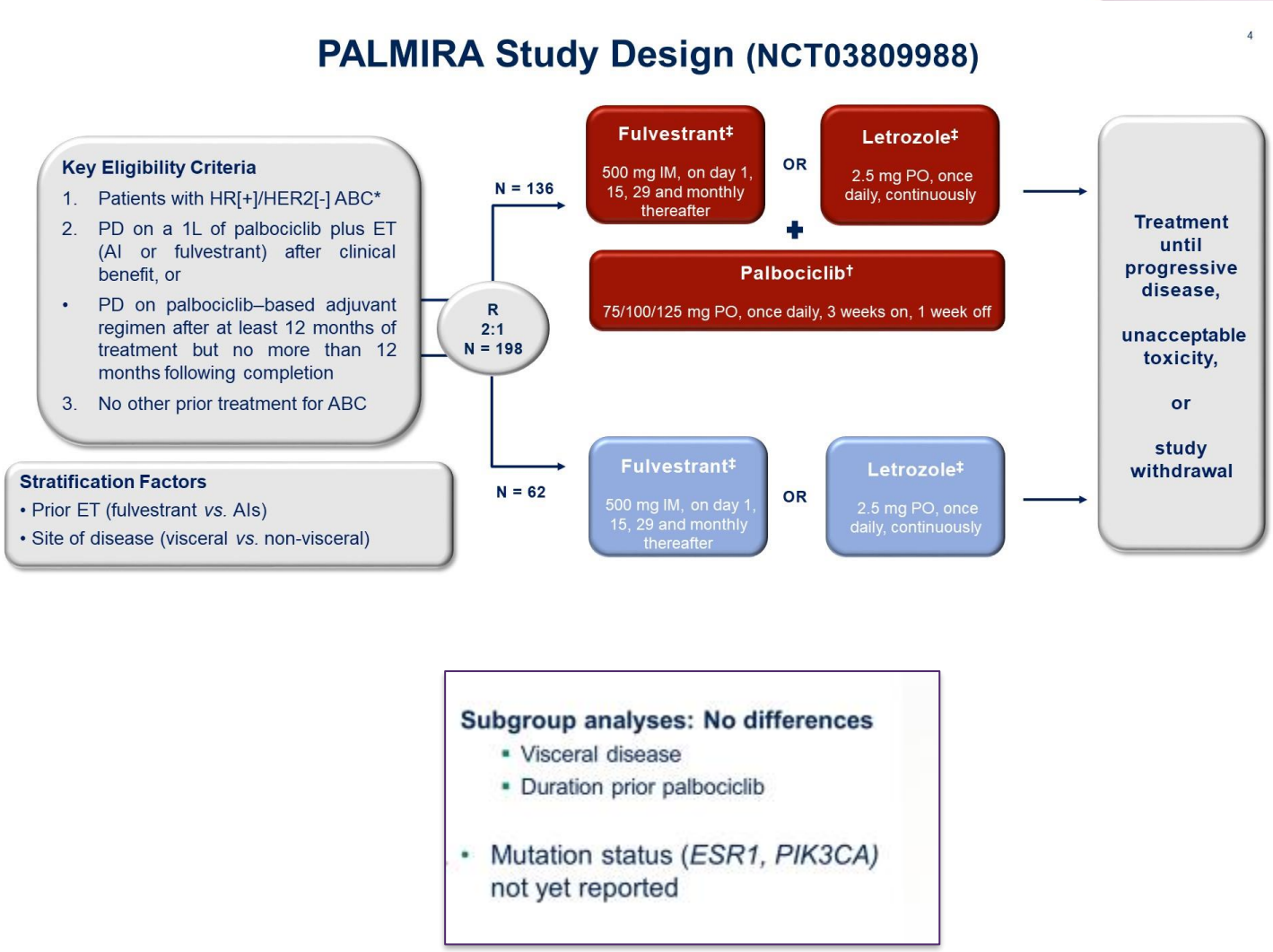
Mayer *SABCS* 2022

Non-significant PFS benefit in palbociclib group

Stover D, ASCO 2023

Can endocrine therapy switch extend CDK4/6i?

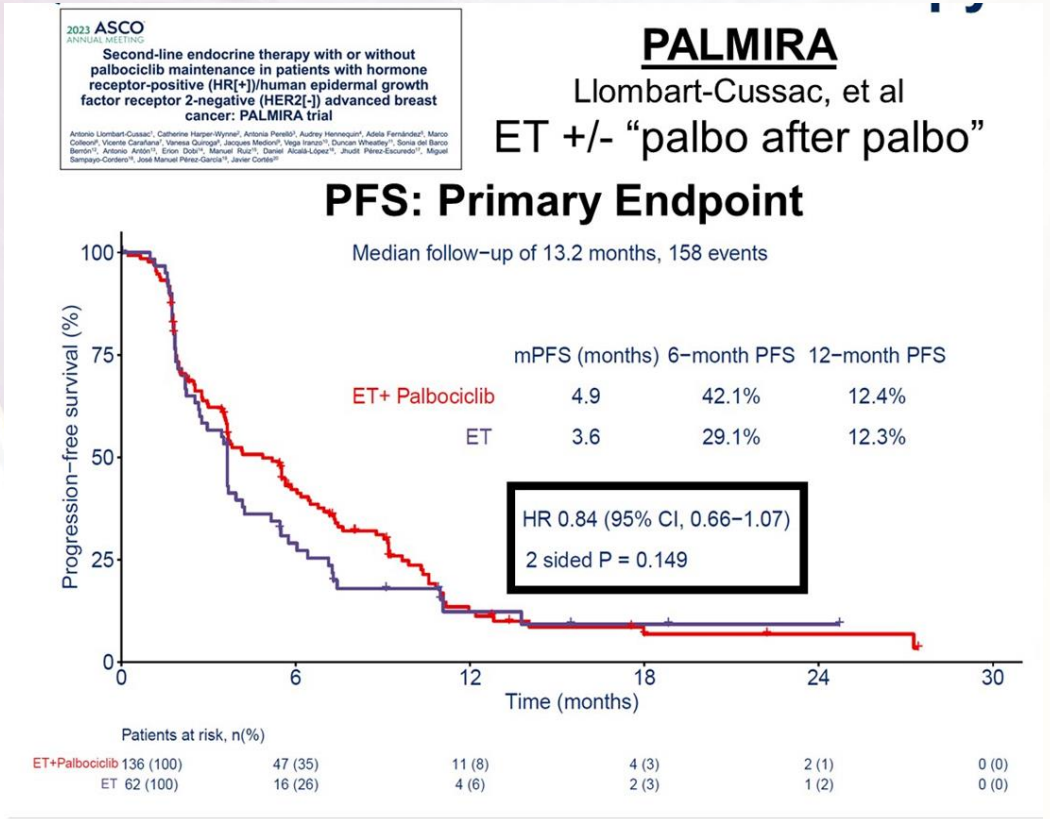
PALMIRA Study



Subgroup analyses: No differences

- Visceral disease
- Duration prior palbociclib

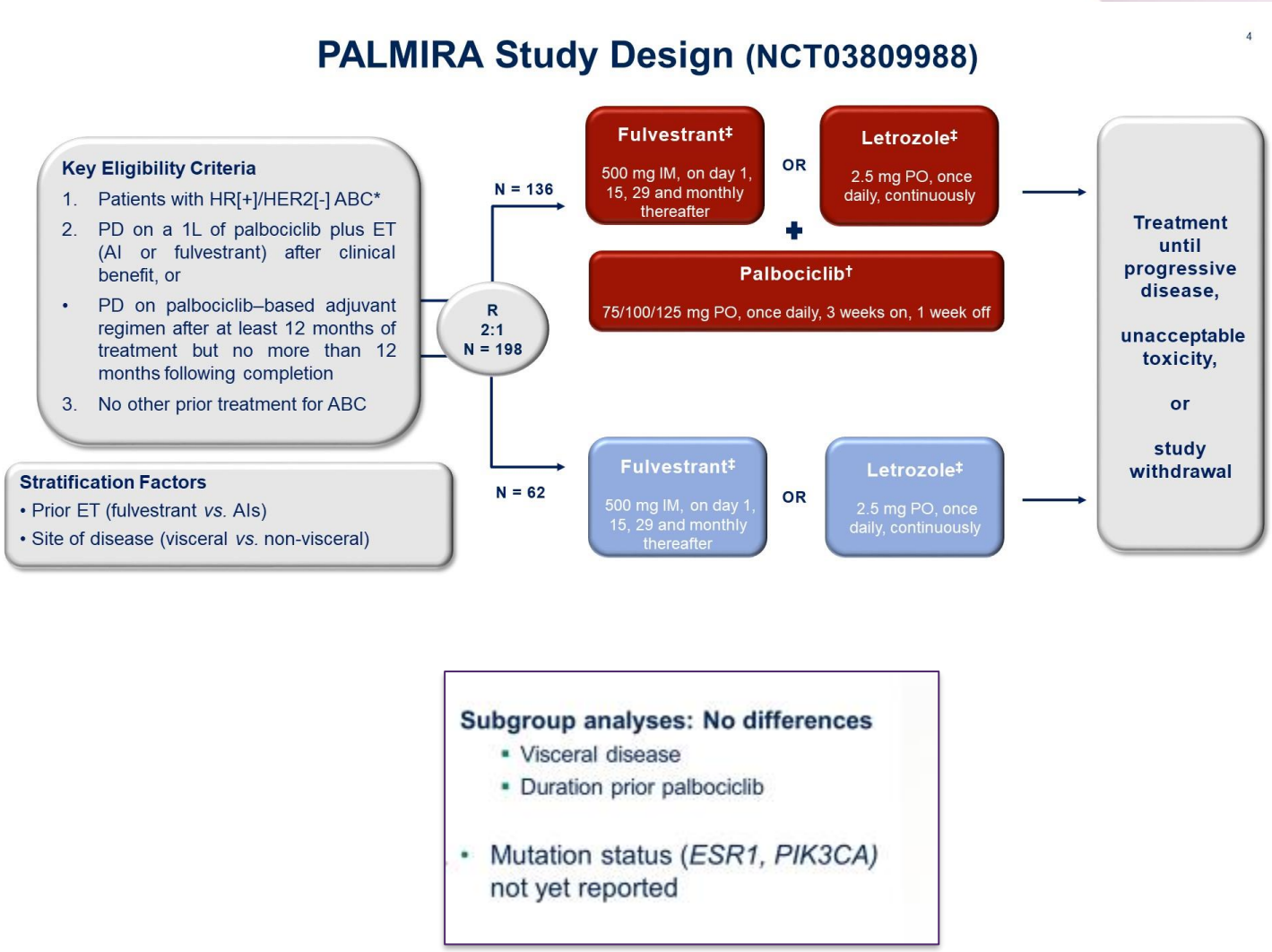
- Mutation status (*ESR1, PIK3CA*) not yet reported



Llombart A, ASCO 2023

Can endocrine therapy switch extend CDK4/6i?

PALMIRA Study



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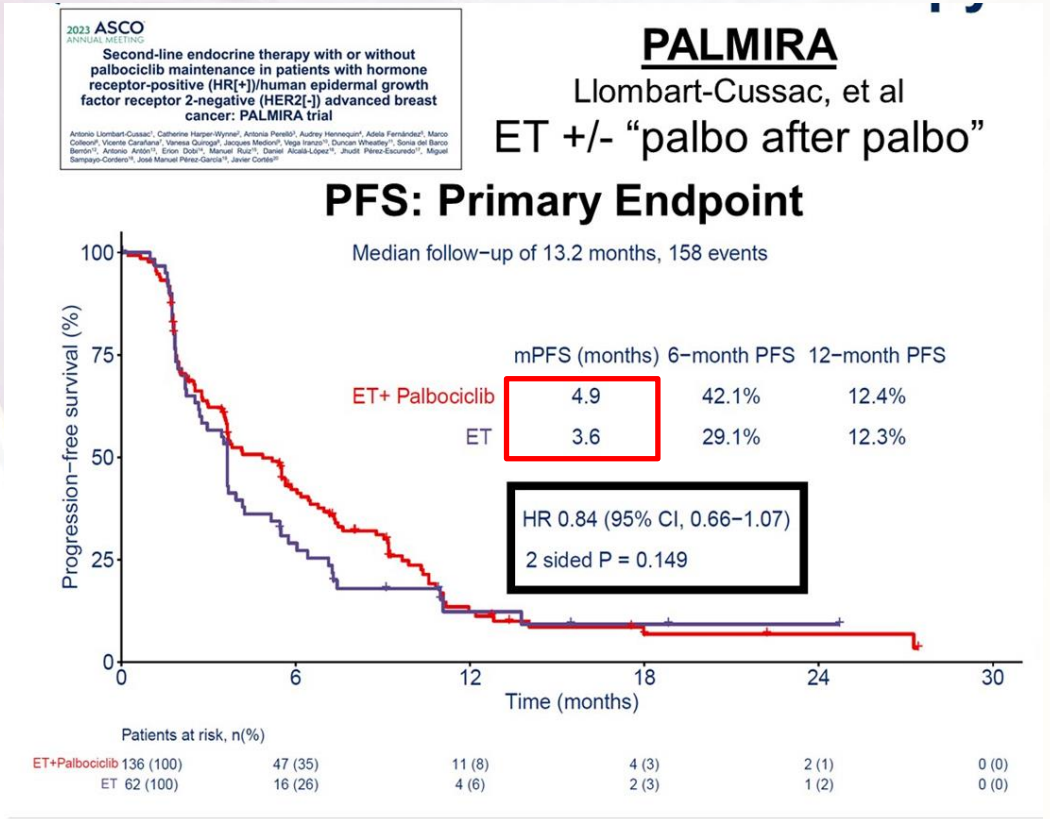


Llombart A, ASCO 2023

Can endocrine therapy switch extend CDK4/6i?

	MAINTAIN	PACE	PALMIRA
Patients (n)	120	166	198
1st line CDK4/6i	Palbociclib (84%)	Palbociclib (90%)	Palbociclib (100%)
% 1st line CDK4/6i >12mo	67%	75%	86%
Endocrine therapy	Fulvestrant (83%) or exemestane	Fulvestrant (100%)	Fulvestrant (90%) or letrozole
'Continuation' CDK4/6i	Ribociclib	Palbociclib	Palbociclib
PFS ET only	**2.8mo**	**4.8mo**	**3.6mo**
PFS Fulv + CDK4/6i	**5.3mo**	**4.6mo**	**4.9mo**

Different studies, different designs, different study populations, different subgroup definitions

Kalinsky JCO 2023; Mayer SABCS 2022; Llombart-Cussac ASCO 2023

Benefit of early switch based on ESR1mut ctDNA?

PADA-1 Trial

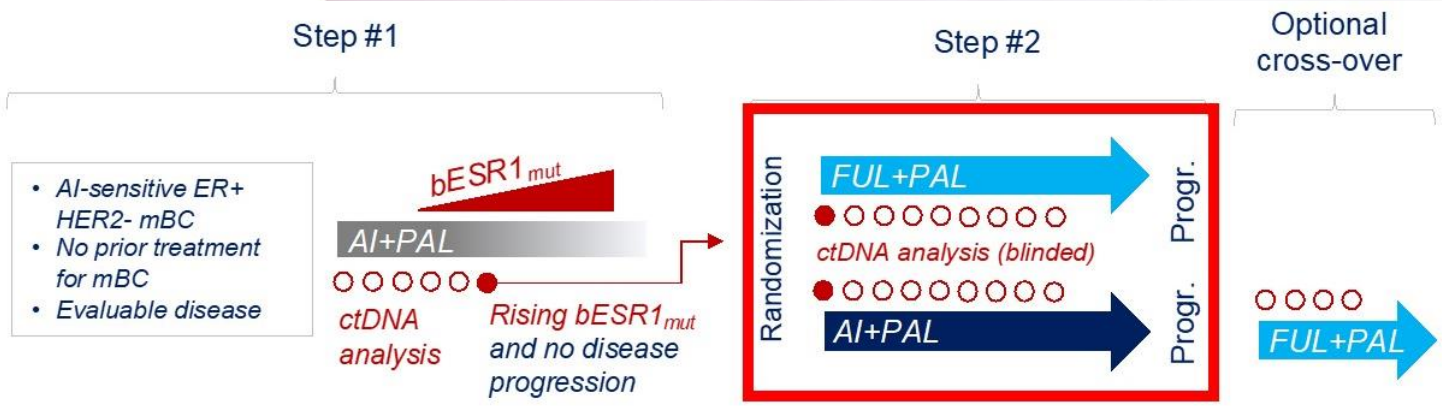
PADA-1 Trial

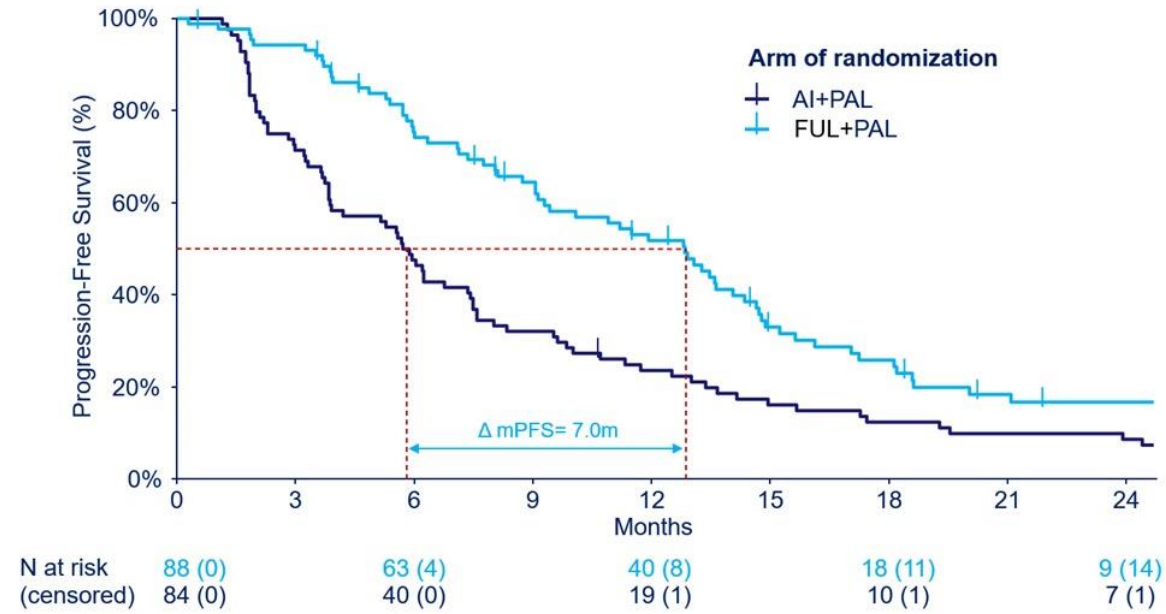
Bidard, et al

Dynamics and type of *ESR1* mutations under AI or fulvestrant combined with palbociclib after randomization in the PADA-1 trial

L Cabel, S Delaloge, AC Hardy-Bessard, F André, T Bachelot, I Bièche, C Callens, A Pradines, F Clatot, T de la Motte Rouge, JL Canon, L Arnould, B Pistilli, F Dalenc, R Sabatier, J Ferrero, A Lortholary, J Lemonnier, F Berger, FC Bidard

UCBG GINECO





Updated Results: PFS1

FUL+PAL mPFS: 12.8 months, 95%CI [9.3;14.7]

AI+PAL mPFS: 5.8 months, 95%CI [3.9;7.5]

PFS HR= 0.54 [0.38;0.75]

Optional cross-over (N=49 patients)

mPFS: 3.5 months, 95%CI [2.4;5.4]

Bidard FC, ASCO 2023

Benefit of early switch based on ESR1mut ctDNA?

PADA-1 Trial

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Bidard, et al

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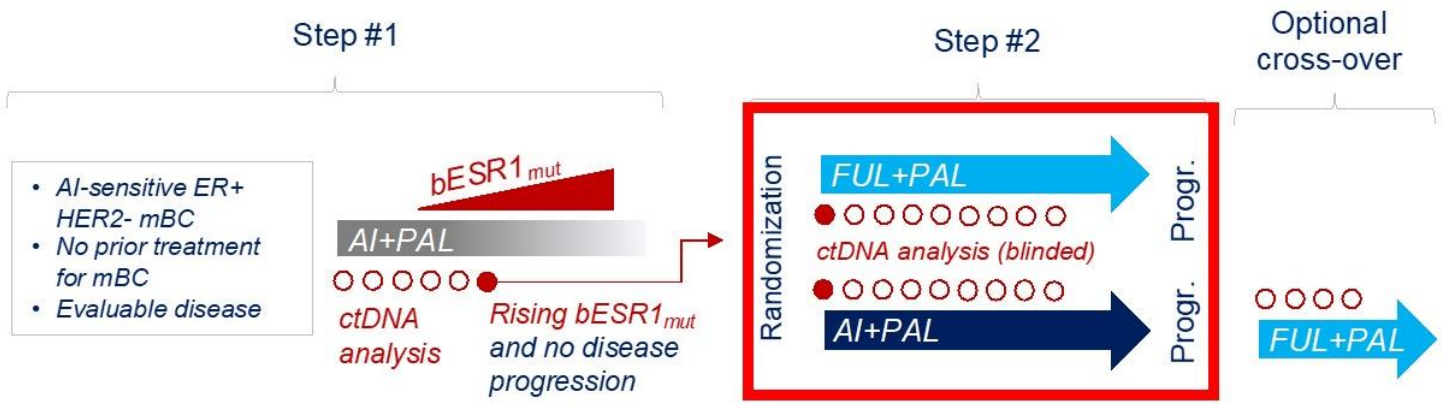
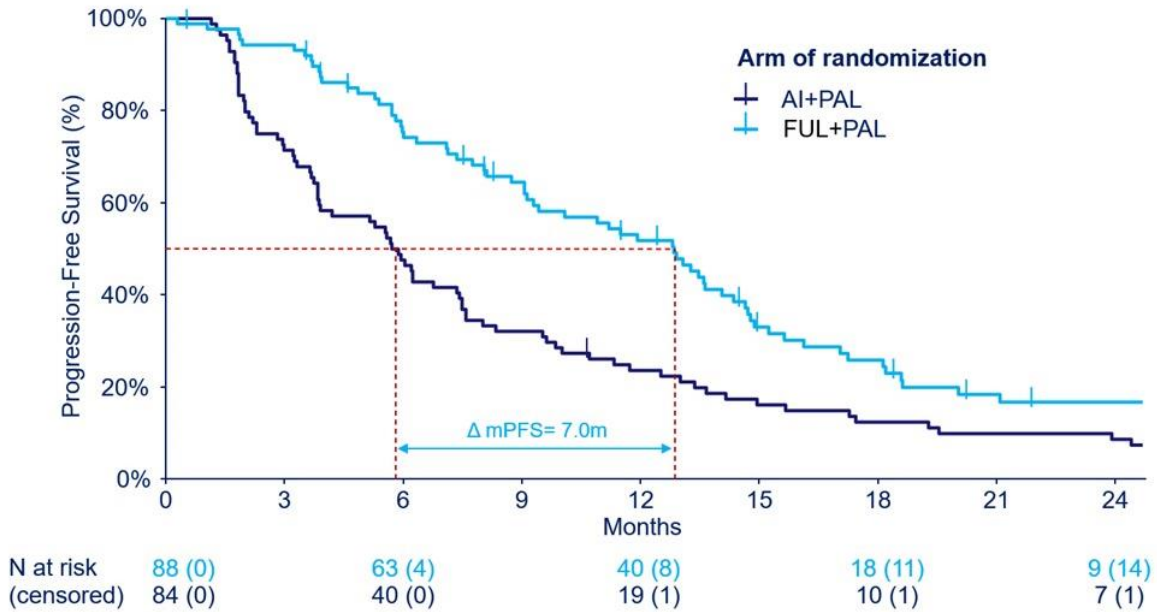
UCBG GINECO





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Δ 7 m

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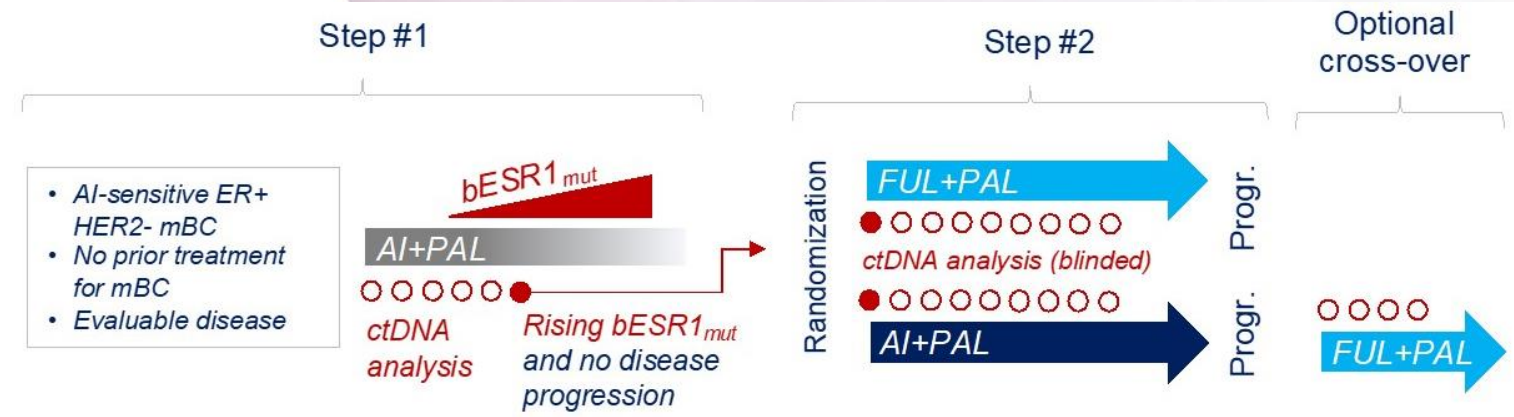
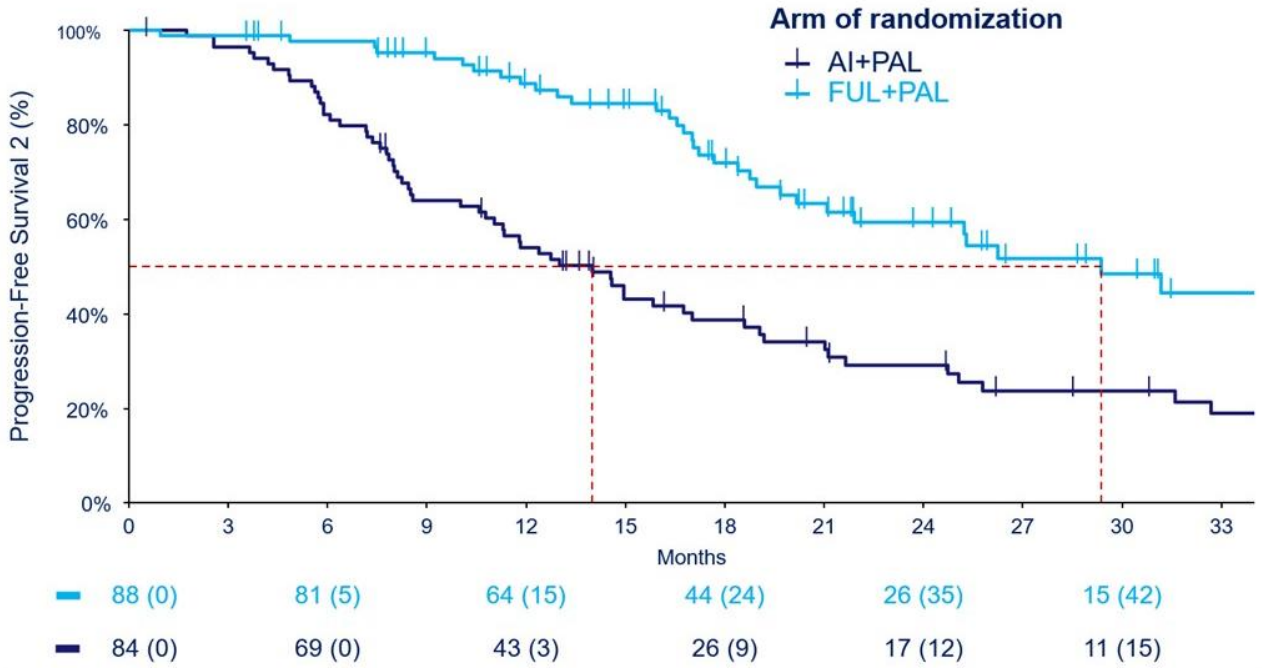
Bidard FC, ASCO 2023

Benefit of early switch based on ESR1mut ctDNA?

PADA-1 Trial results





Updated Results: PFS2

FUL+PAL mPFS2: 29.4 months, 95%CI [21.9;NR]

AI+PAL mPFS2: 14.0 months, 95%CI [11.0;18.6]

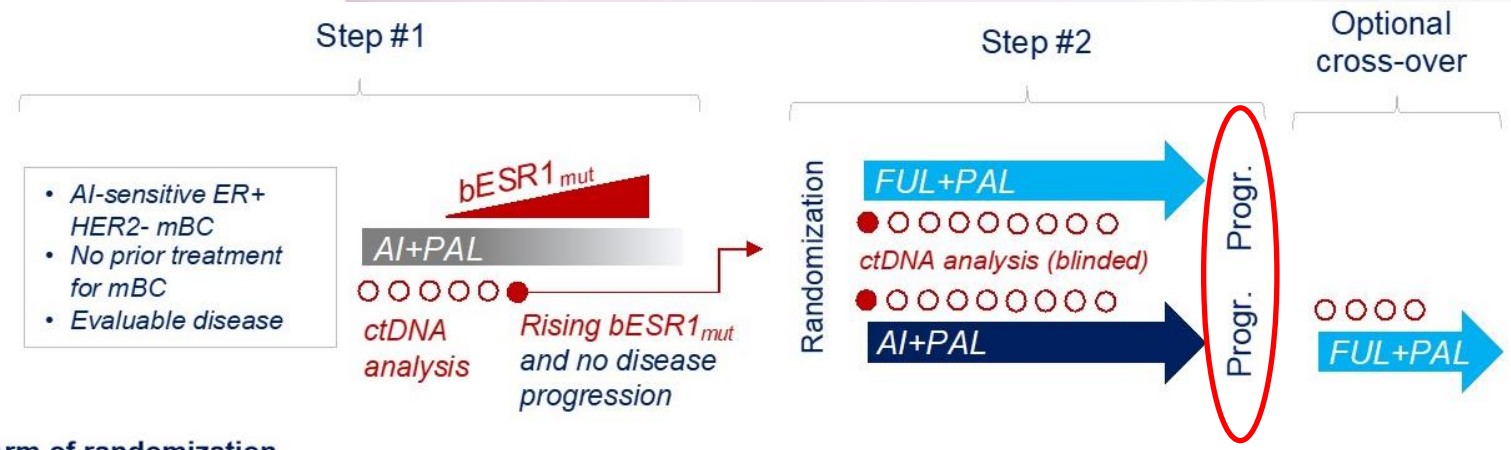
PFS2 HR= 0.37 [0.24;0.56]

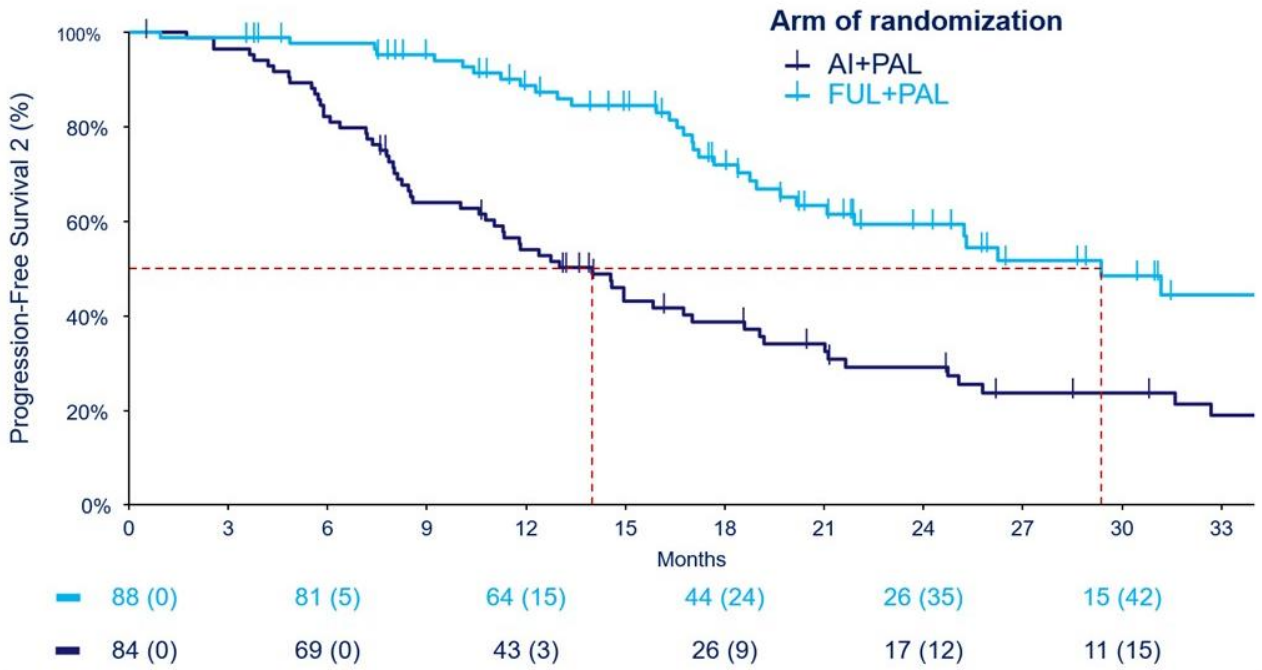
Await overall survival data

Bidard FC , ASCO 2023

Benefit of early switch based on ESR1mut ctDNA?

PADA-1 Trial results





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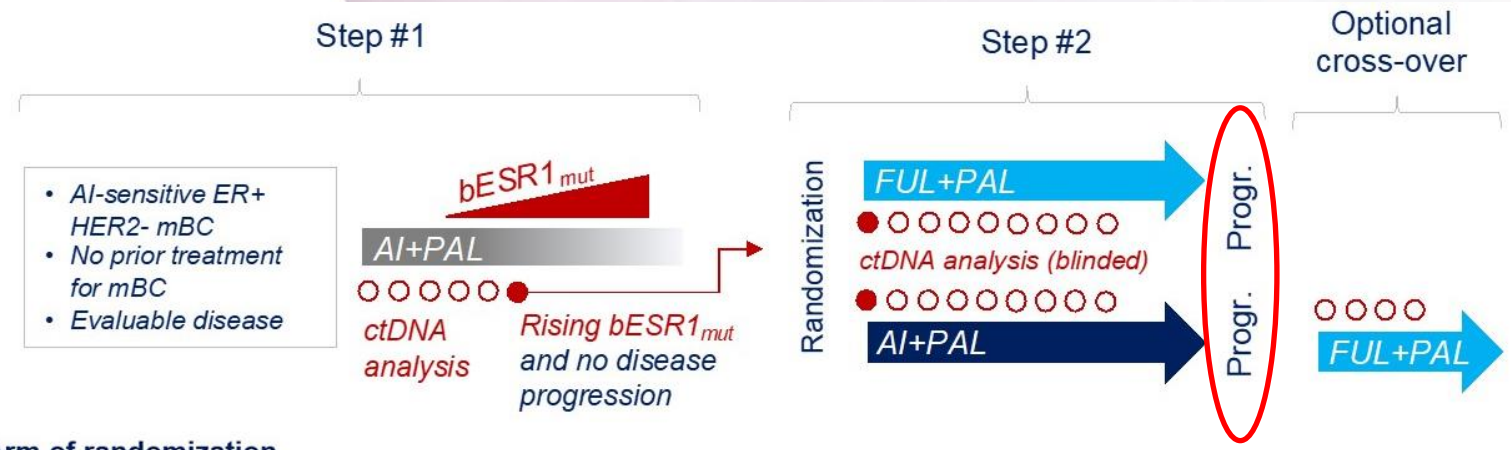
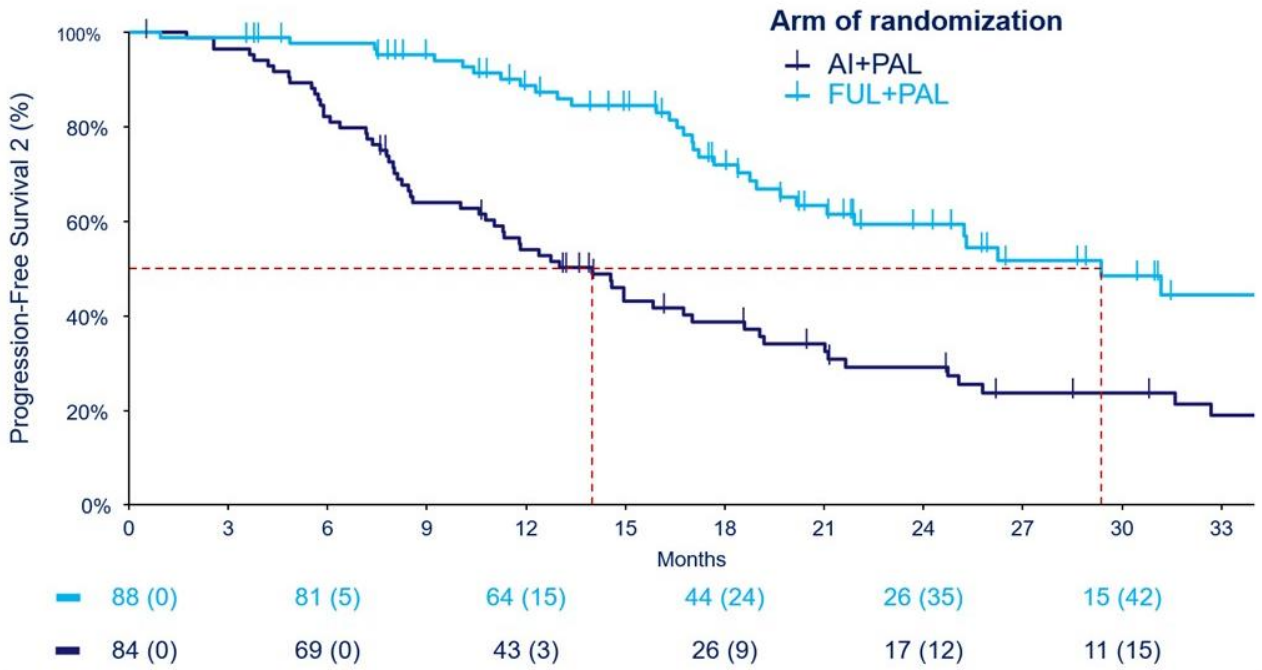
Bidard FC , ASCO 2023

Benefit of early switch based on ESR1mut ctDNA?

PADA-1 Trial results





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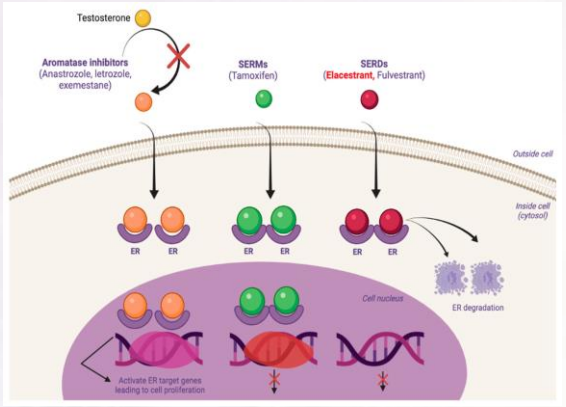
PFS2 HR= 0.37 [0.24;0.56]

Δ 15,4 m

Await overall survival data

Bidard FC , ASCO 2023

SERDs



	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

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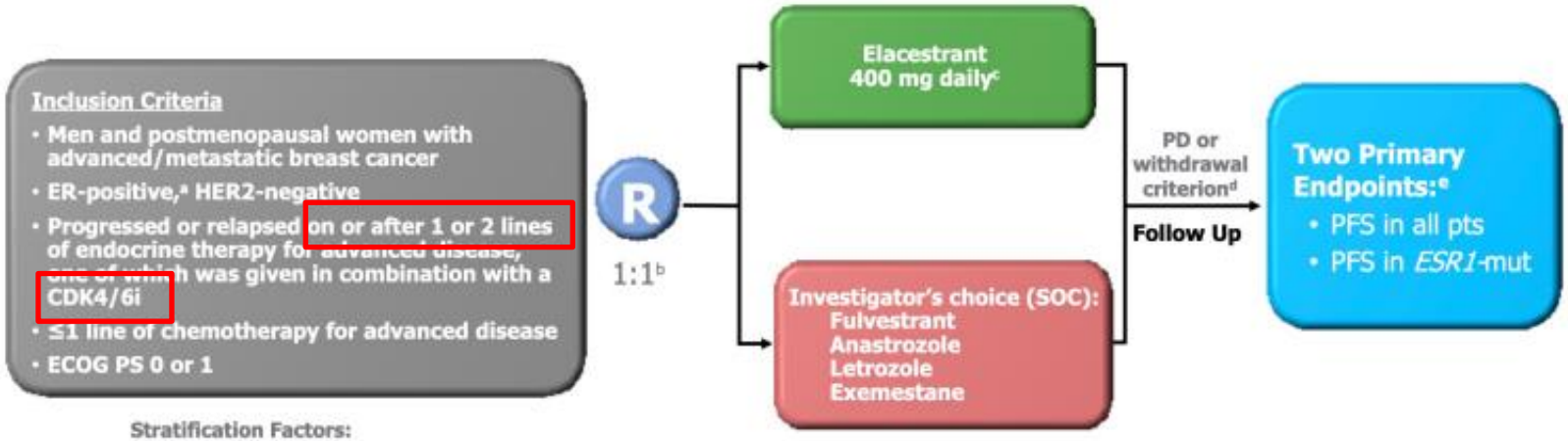
EMERALD trial: Elacestrant



Parameter	Elacestrant		SOC	
	All (N=239)	*ESR1*-mut (N=115)	All (N=239)	*ESR1*-mut (N=113)
Prior CDK4/6i, n (%)	**239 (100)**	**115 (100)**	**239 (100)**	**113 (100)**
Visceral metastasis*, n (%)	**163 (68.2)**	**81 (70.4)**	**170 (71.1)**	**84 (74.3)**
Number of prior lines of endocrine therapy, n (%)**				
1	129 (54.0)	73 (63.5)	142 (59.4)	69 (61.1)
2	**110 (46.0)**	**42 (36.5)**	**97 (40.6)**	**44 (38.9)**
Type of prior endocrine therapy, n (%)**				
Fulvestrant	**70 (29.3)**	**27 (23.5)**	**75 (31.4)**	**28 (24.8)**
AI	193 (80.8)	101 (87.8)	194 (81.2)	96 (85.0)
Tamoxifen	19 (7.9)	9 (7.8)	15 (6.3)	9 (8.0)
Number of prior lines of chemotherapy, n (%)**				
0	191 (79.9)	89 (77.4)	180 (75.3)	81 (71.7)
1	**48 (20.1)**	**26 (22.6)**	**59 (24.7)**	**32 (28.3)**

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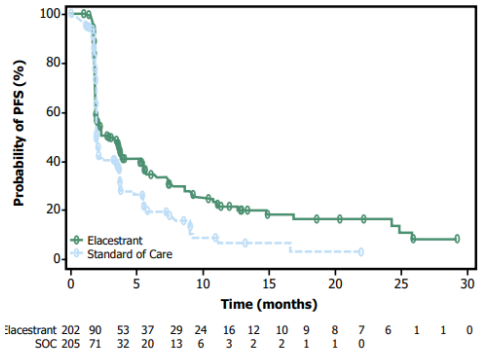
EMERALD results

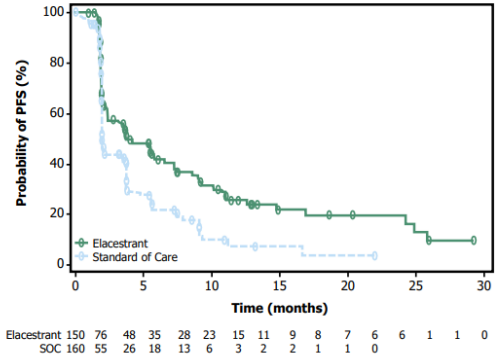
All Patients: PFS by Duration of CDK4/6i

At least 6 mo CDK4/6i



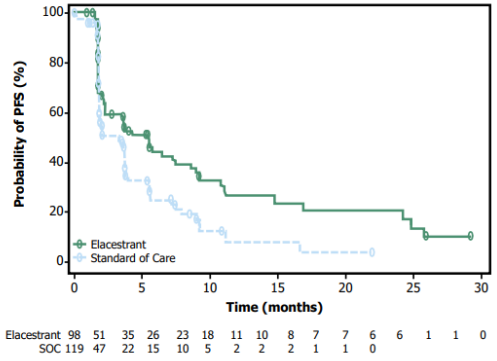
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**2.79** (1.94 - 3.78)	**1.91** (1.87 - 2.14)
PFS rate at 12 months, % (95% CI)	21.00 (13.57 - 28.43)	6.42 (0.75 - 12.09)
Hazard ratio (95% CI)	**0.688** (0.535 - 0.884)	

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)	

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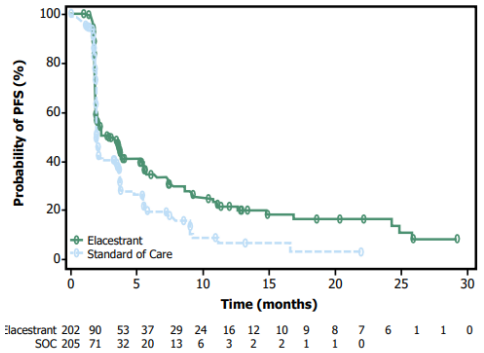
EMERALD results

All Patients: PFS by Duration of CDK4/6i

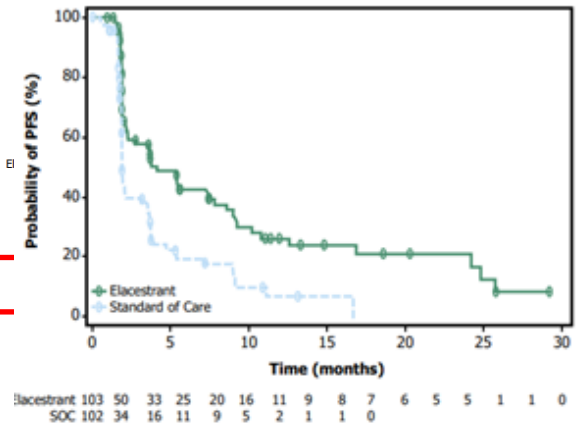
At least 6 mo CDK4/6i



	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)	

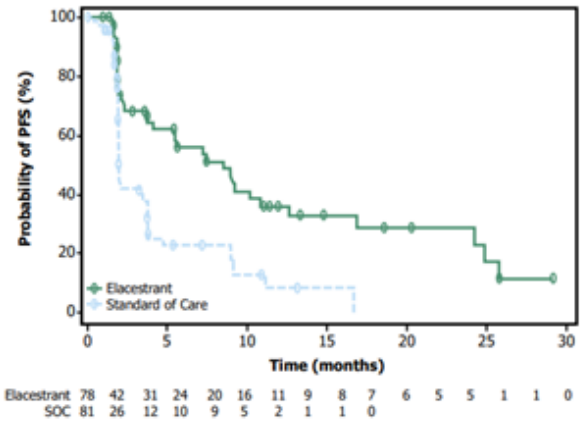
Patients with *ESR1*-mut Tumors: PFS by Duration of CDK4/6i

At least 6 mo CDK4/6i



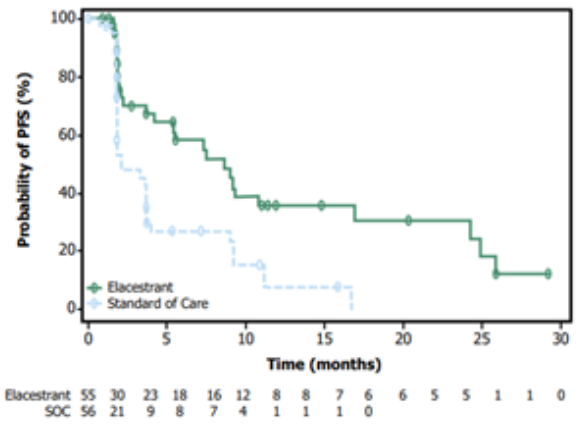
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

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)	

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SERENA -2 trial: Camizestrant

Design

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

No era mandatorio el uso de iCDK previo

Post-menopausal ER+/HER2- ABC candidates to receive fulvestrant monotherapy in the ABC setting

Stratification: Prior CDK4/6i Lung/liver mets

R

1:1:1:1
N=240

- camizestrant 300 mg (n=20) (CSP v5 amendment: 16Dec20)
- camizestrant 75 mg (n=74)
- camizestrant 150 mg (n=73)
- fulvestrant (n=73)

- **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 was designed to compare each of the camizestrant 75, 150 and 300 mg doses with fulvestrant
- No formal analyses of camizestrant 300 mg versus fulvestrant were conducted since enrolment to camizestrant 300 mg was stopped early (n=20 patients)
- SERENA-2 was not powered to compare between camizestrant doses

Key baseline patient characteristics

	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)

ESR1m detectable 36,7%
Prior CDK4/6i 49,6%

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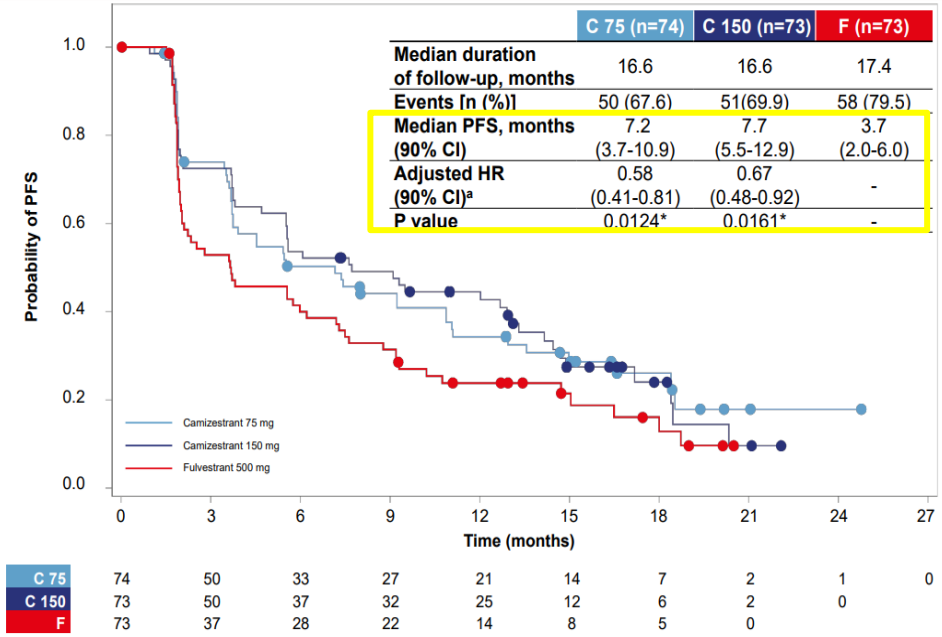
SERENA -2 trial: PFS

Primary endpoint: PFS by investigator



	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*	-

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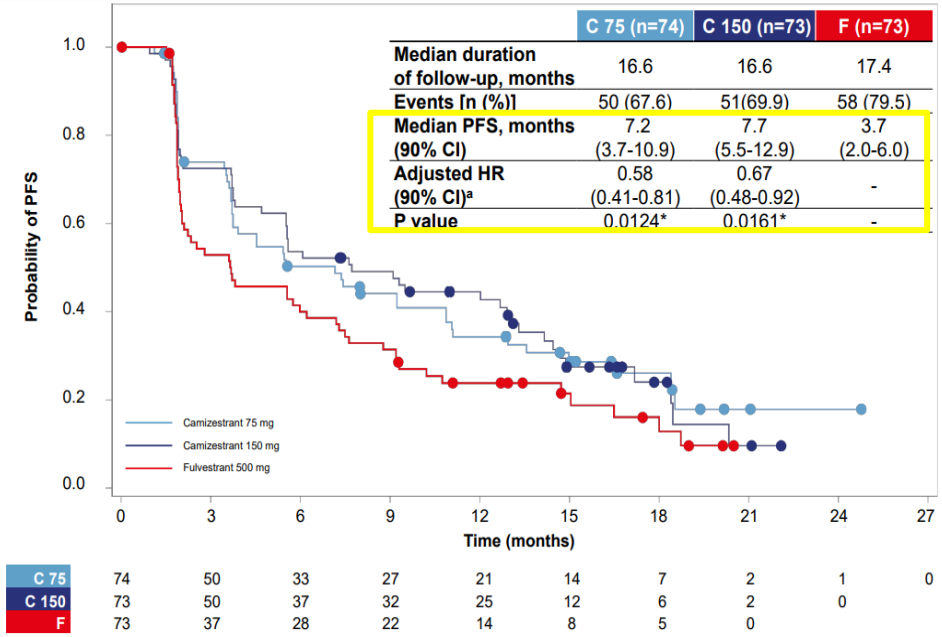
SERENA -2 trial: PFS

Primary endpoint: PFS by investigator



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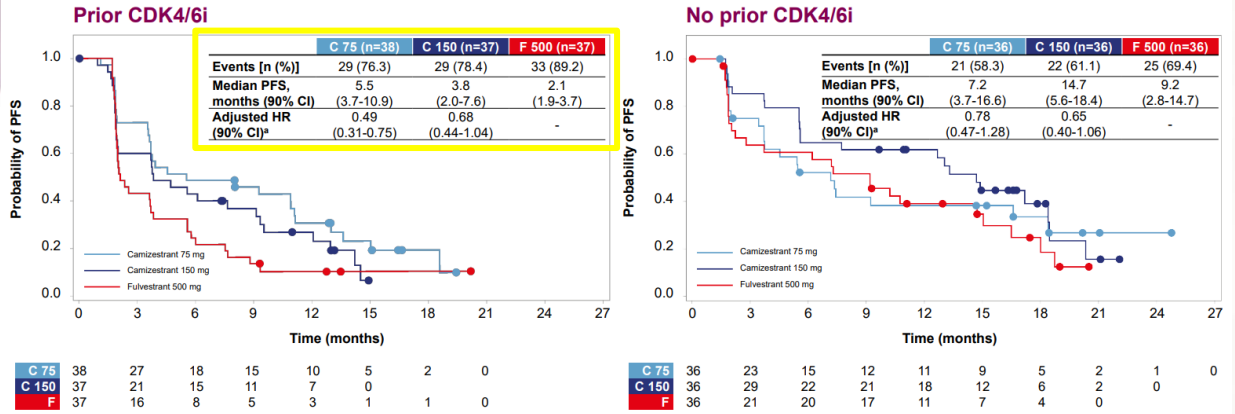
Adjusted HR (90% CI)[a]	0.58 (0.41-0.81)	0.67 (0.48-0.92)	-
P value	0.0124*	0.0161*	-

PFS in patients by prior use of 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)	-

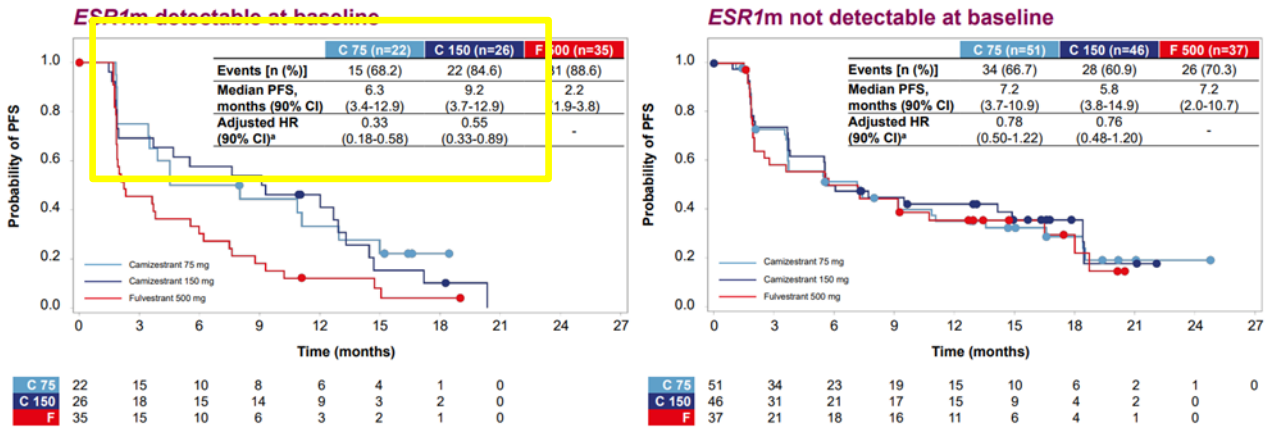
	C 75 (n=36)	C 150 (n=36)	F 500 (n=36)
Events [n (%)]	21 (58.3)	22 (61.1)	25 (69.4)
Median PFS, months (90% CI)	7.2 (3.7-16.6)	14.7 (5.6-18.4)	9.2 (2.8-14.7)
Adjusted HR (90% CI)[a]	0.78 (0.47-1.28)	0.65 (0.40-1.06)	-

- 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

PFS in patients by detectable *ESR1*m



	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 (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)	-

- 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

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CAPItello-291: Study overview

Phase III, randomized, double-blind, placebo-controlled study (NCT04305496)

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*

HER2– was defined as IHC 0 or 1+, or IHC 2+/ISH–. *Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia vs Reg
ABC, advanced (locally advanced [inoperable] or metastatic) breast cancer.
Pre- or peri-menopausal women also received a luteinizing hormone-releasing hormone agonist for the duration of the study treatment

Dual primary endpoints

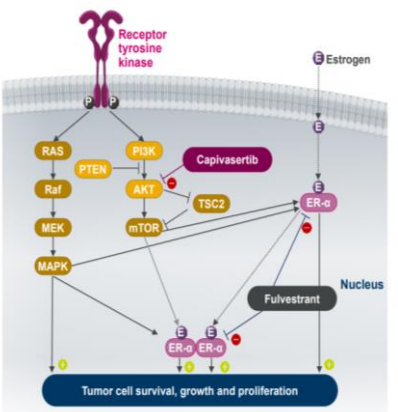
PFS by investigator assessment
- Overall
- AKT pathway-altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

Key secondary endpoints

Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

- AKT pathway activation occurs in many HR+/HER2– ABC through alterations in *PIK3CA, AKT1 and PTEN*, but may also occur in cancers without those genetic alterations.[1,2] AKT signalling is also implicated in the development of resistance to endocrine therapy[2]
- Capivasertib is a potent, selective inhibitor of all three AKT isoforms (AKT1/2/3)
- In the Phase II, placebo-controlled FAKTION trial[3]:
  - The addition of capivasertib to fulvestrant significantly improved PFS and OS in postmenopausal women with AI-resistant HR+/HER2– ABC in the overall population, with a more pronounced benefit in pathway altered tumours
  - No patients had received prior CDK4/6 inhibitors



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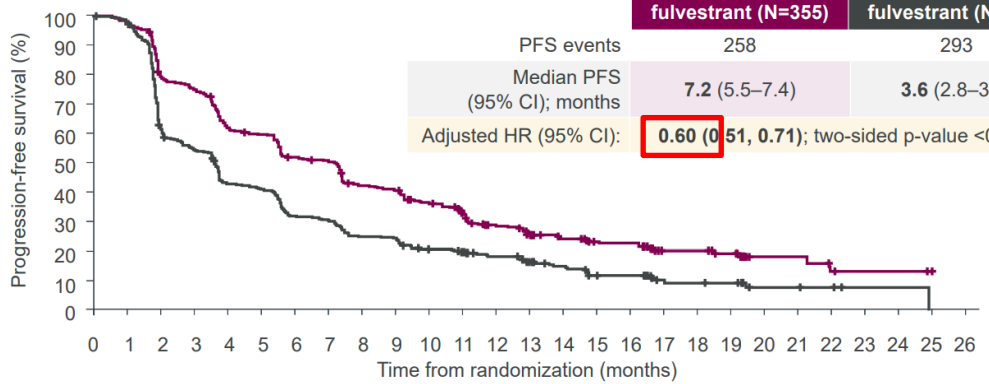
CAPItello-291: results

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)
Metastatic sites; n (%)	Bone only	51 (14.4)	52 (14.7)	25 (16.1)	16 (11.9)
	Liver*	156 (43.9)	150 (42.5)	70 (45.2)	53 (39.6)
	Visceral	237 (66.8)	241 (68.3)	103 (66.5)	98 (73.1)

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.

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CAPItello-291: results

Characteristic		Overall population: Capivasertib + fulvestrant (N=355)	Overall population: Placebo + fulvestrant (N=353)	AKT pathway-altered population: Capivasertib + fulvestrant (N=155)	AKT pathway-altered population: 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)
Metastatic sites; n (%)	Bone only	51 (14.4)	52 (14.7)	25 (16.1)	16 (11.9)
	Liver*	156 (43.9)	150 (42.5)	70 (45.2)	53 (39.6)
	Visceral	237 (66.8)	241 (68.3)	103 (66.5)	98 (73.1)

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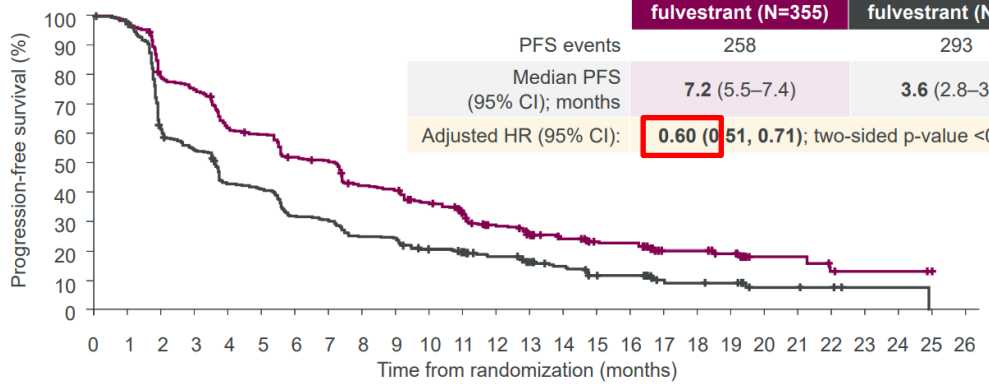


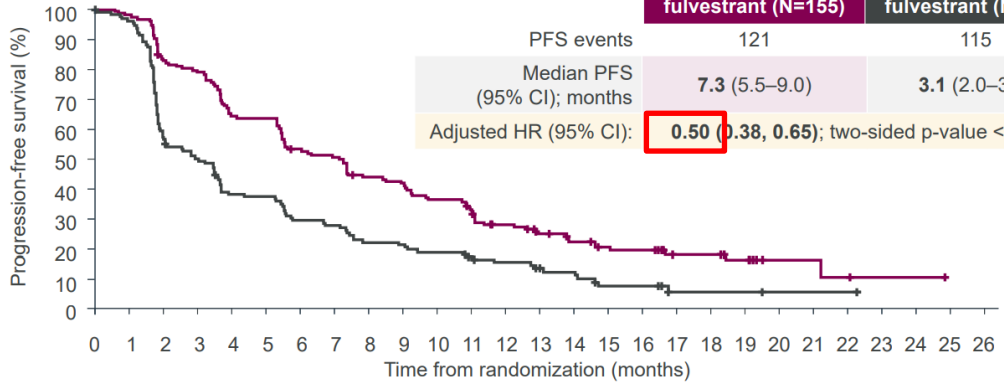
Number of patients at risk

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.

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.

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TROPiCS-02

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

- At least 1 endocrine therapy, taxane, and CDK4/6 inhibitor 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

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[b]
(capecitabine, vinorelbine, gemcitabine, or eribulin)
n=271

Endpoints

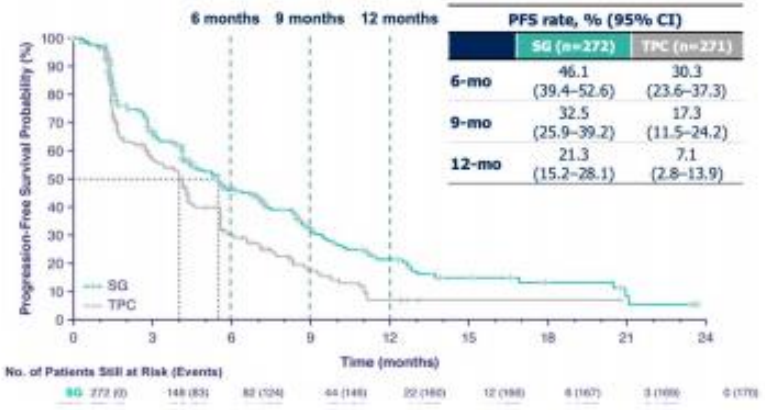
Primary
- PFS by BICR

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

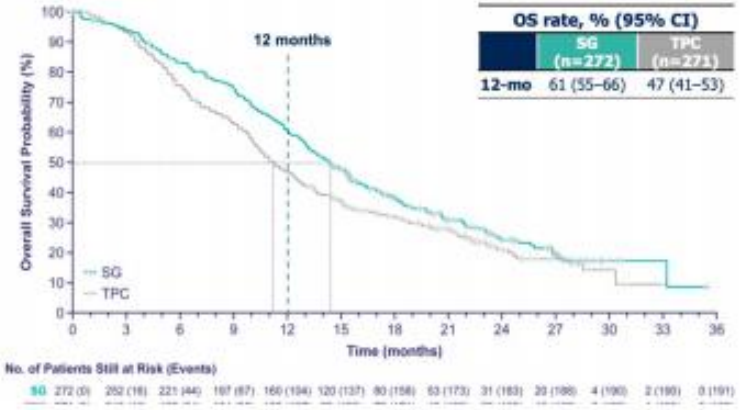
BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	*P*=0.0003	



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)

OS

	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)

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TROPiCS-02

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

- At least 1 endocrine therapy, taxane, and CDK4/6 inhibitor 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

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[b]
(capecitabine, vinorelbine, gemcitabine, or eribulin)
n=271

Endpoints

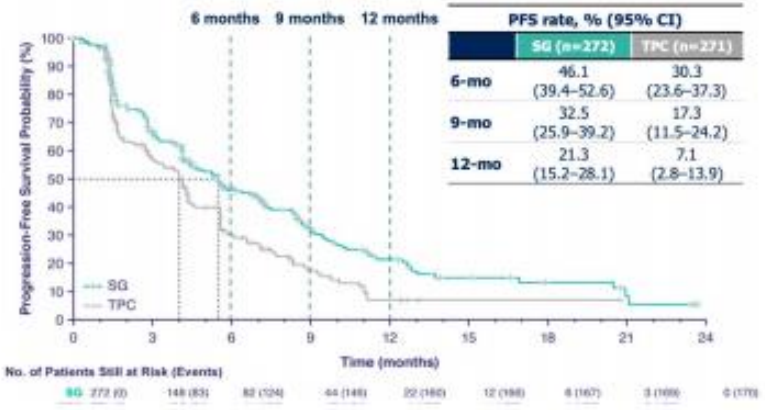
Primary
- PFS by BICR

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

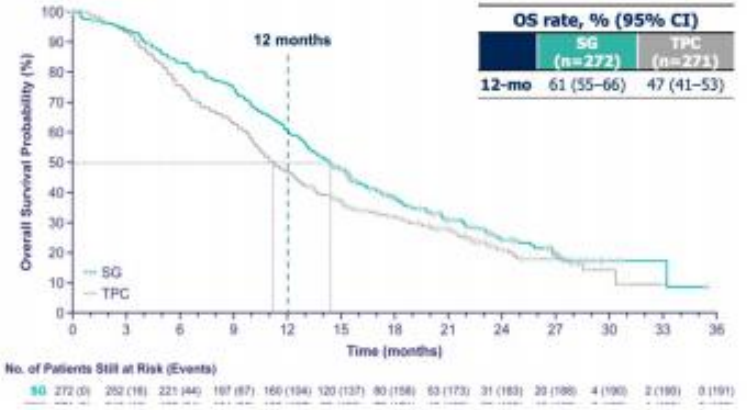
BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	*P*=0.0003	



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)

OS

	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)

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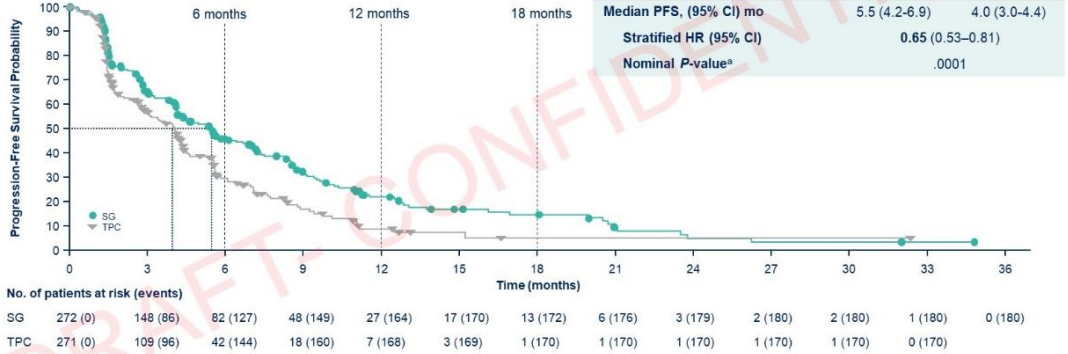
TROPiCS-02

Progression-Free Survival



BICR analysis	SG (n = 272)	TPC (n = 271)
Median PFS, (95% CI) mo	5.5 (4.2-6.9)	4.0 (3.0-4.4)
Stratified HR (95% CI)	**0.65** (0.53–0.81)	
Nominal *P*-value[a]	.0001	

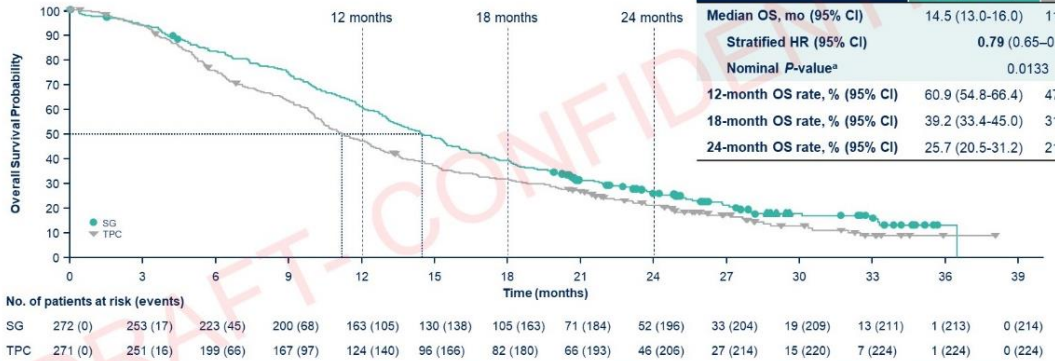
No. of patients at risk (events)

SG	272 (0)	148 (86)	82 (127)	48 (149)	27 (164)	17 (170)	13 (172)	6 (176)	3 (179)	2 (180)	2 (180)	1 (180)	0 (180)
TPC	271 (0)	109 (96)	42 (144)	18 (160)	7 (168)	3 (169)	1 (170)	1 (170)	1 (170)	1 (170)	1 (170)	0 (170)	

SG continued to demonstrate improvement in PFS vs TPC at longer follow-up, with 35% reduction in risk of disease progression or death, and a higher proportion of patients remained alive and progression-free at each landmark

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
[a]Stratified log rank *P*-value.

Overall Survival



	SG (n = 272)	TPC (n = 271)
Median OS, mo (95% CI)	14.5 (13.0-16.0)	11.2 (10.2-12.6)
Stratified HR (95% CI)	**0.79** (0.65–0.95)	
Nominal *P*-value[a]	0.0133	
12-month OS rate, % (95% CI)	60.9 (54.8-66.4)	47.1 (41.0-53.0)
18-month OS rate, % (95% CI)	39.2 (33.4-45.0)	31.7 (26.2-37.4)
24-month OS rate, % (95% CI)	25.7 (20.5-31.2)	21.1 (16.3-26.3)

No. of patients at risk (events)

SG	272 (0)	253 (17)	223 (45)	200 (68)	163 (105)	130 (138)	105 (163)	71 (184)	52 (196)	33 (204)	19 (209)	13 (211)	1 (213)	0 (214)
TPC	271 (0)	251 (16)	199 (66)	167 (97)	124 (140)	96 (166)	82 (180)	66 (193)	46 (206)	27 (214)	15 (220)	7 (224)	1 (224)	0 (224)

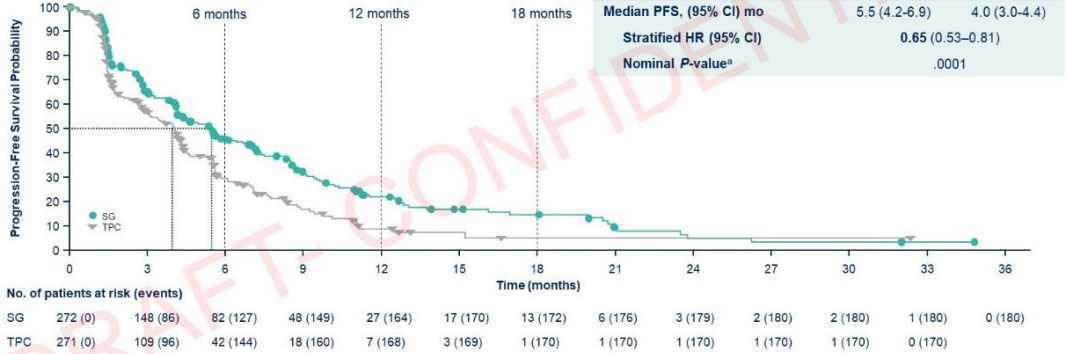
SG continued to demonstrate improvement in OS vs TPC at longer follow-up, with 21% reduction in risk of death and a higher proportion of patients remaining alive at each landmark

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
[a]Stratified log rank *P*-value.

S. Tolaney, ASCO 2023

TROPiCS-02

Progression-Free Survival



BICR analysis	SG (n = 272)	TPC (n = 271)
Median PFS, (95% CI) mo	5.5 (4.2-6.9)	4.0 (3.0-4.4)
Stratified HR (95% CI)	**0.65** (0.53–0.81)	
Nominal *P*-value[a]	.0001	

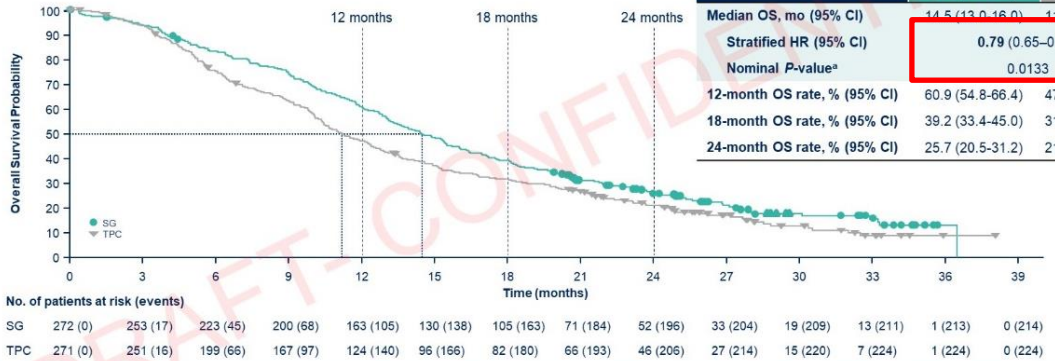
No. of patients at risk (events)

SG	272 (0)	148 (86)	82 (127)	48 (149)	27 (164)	17 (170)	13 (172)	6 (176)	3 (179)	2 (180)	2 (180)	1 (180)	0 (180)
TPC	271 (0)	109 (96)	42 (144)	18 (160)	7 (168)	3 (169)	1 (170)	1 (170)	1 (170)	1 (170)	1 (170)	0 (170)	

SG continued to demonstrate improvement in PFS vs TPC at longer follow-up, with 35% reduction in risk of disease progression or death, and a higher proportion of patients remained alive and progression-free at each landmark

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
[a]Stratified log rank *P*-value.

Overall Survival



	SG (n = 272)	TPC (n = 271)
Median OS, mo (95% CI)	14.5 (13.0-16.0)	11.2 (10.2-12.6)
Stratified HR (95% CI)	**0.79** (0.65–0.95)	
Nominal *P*-value[a]	0.0133	
12-month OS rate, % (95% CI)	60.9 (54.8-66.4)	47.1 (41.0-53.0)
18-month OS rate, % (95% CI)	39.2 (33.4-45.0)	31.7 (26.2-37.4)
24-month OS rate, % (95% CI)	25.7 (20.5-31.2)	21.1 (16.3-26.3)

No. of patients at risk (events)

SG	272 (0)	253 (17)	223 (45)	200 (68)	163 (105)	130 (138)	105 (163)	71 (184)	52 (196)	33 (204)	19 (209)	13 (211)	1 (213)	0 (214)
TPC	271 (0)	251 (16)	199 (66)	167 (97)	124 (140)	96 (166)	82 (180)	66 (193)	46 (206)	27 (214)	15 (220)	7 (224)	1 (224)	0 (224)

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S. Tolaney, ASCO 2023

Fixed dose Capecitabine

X-7/7 Study Design

ELIGIBILITY

- Adult female patients with pathologically confirmed MBC
- Any prior number of chemo or endocrine therapies
- Any breast cancer subtype
- HER2+ required concurrent trastuzumab
- CrCl >50 mL/min

STRATIFICATION

- Line of chemotherapy (first or subsequent line)
- Measurable or non-measurable disease
- ER status

1:1

FD-7/7 Arm (N=80)

Capecitabine 1500 mg PO BID x7 days followed by 7-day rest

SD-14/7 Arm (N=73)

Capecitabine 1250* mg/m² PO BID x14 days followed by 7-day rest

*Physician had discretion to use alternative dosing of 1000 mg/m² PO BID (N=11)

- CT C/A/P and bone scan every 12 weeks
- Cycles repeated every 14 (FD-7/7) or 21 (SD-14/7) days until PD, unacceptable toxicity, or delays >4 weeks
- Capecitabine toxicities were solicited at each visit

ENDPOINTS

- Primary: 3-month PFS
- Secondary: PFS, Overall Survival, Objective Response Rate, Toxicity

Toxicity

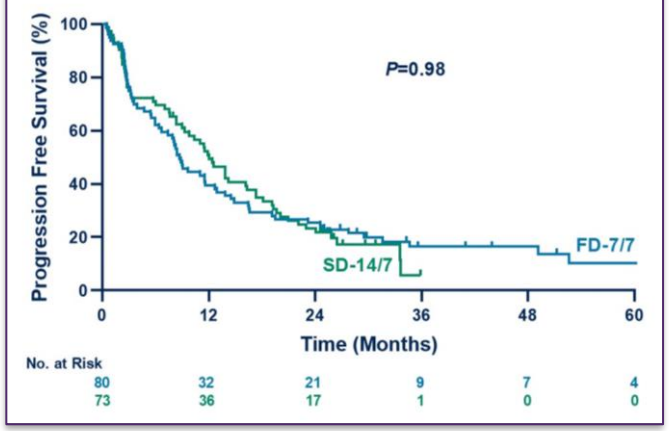
	FD-7/7 (N=80)	SD-14/7 (N=73)	P-Value
Diarrhea			
Any Grade	16 (20)	45 (61.6)	0.0039
Grade 2-4	**2 (2.5)**	**15 (20.5)**	**0.0008**
Hand Foot Syndrome			
Any Grade	22 (27.5)	39 (53.4)	0.0033
Grade 2-4	**3 (3.8)**	**11 (15.1)**	**0.0019**
Oral Mucositis			
Any Grade	3 (3.75)	20 (27.4)	0.0001
Grade 2-4	**0**	**4 (5.5)**	**0.0001**
Neutropenia			
Any Grade	30 (37.5)	31 (42.5)	0.67
Grade 2-4	**17 (21.3)**	**20 (27.4)**	0.68

Grade 3-4 toxicity:
27.4% in SD-14/7
11.3% in FD-7/7
p=0.02

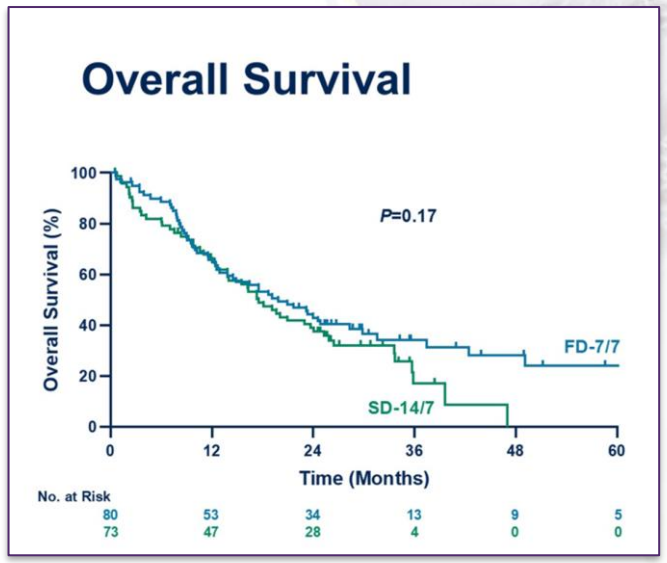
Treatment Discontinuation:
28.7% in SD-14/7
7.5% in FD-7/7
p<0.0006

Dose Modification:
23.3% in SD-14/7
7.5% in FD-7/7
p=0.0063

Progression Free Survival



Overall Survival



Qamar Khan, MD. ASCO 2023

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ENDPOINTS
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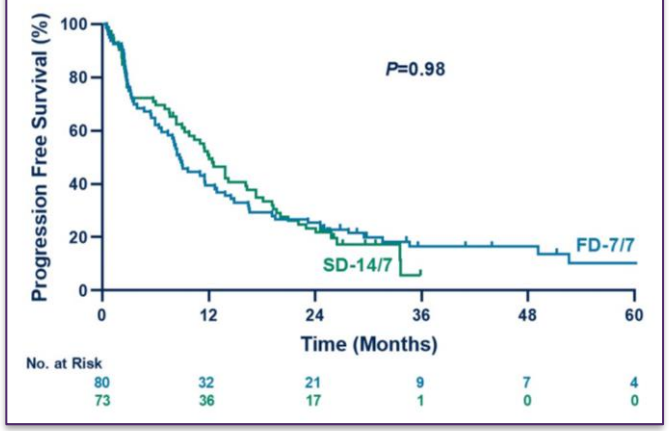
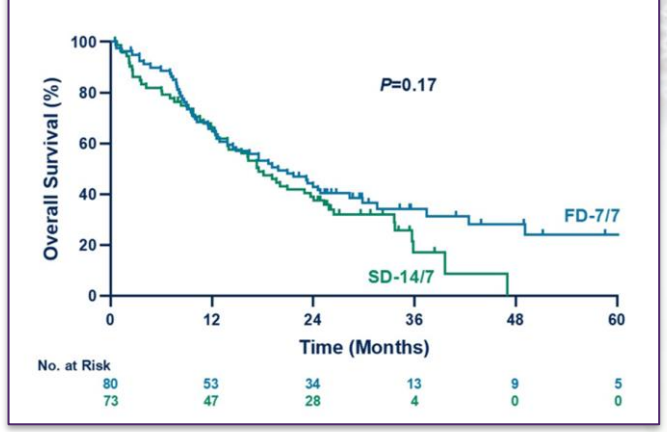
Progression Free Survival



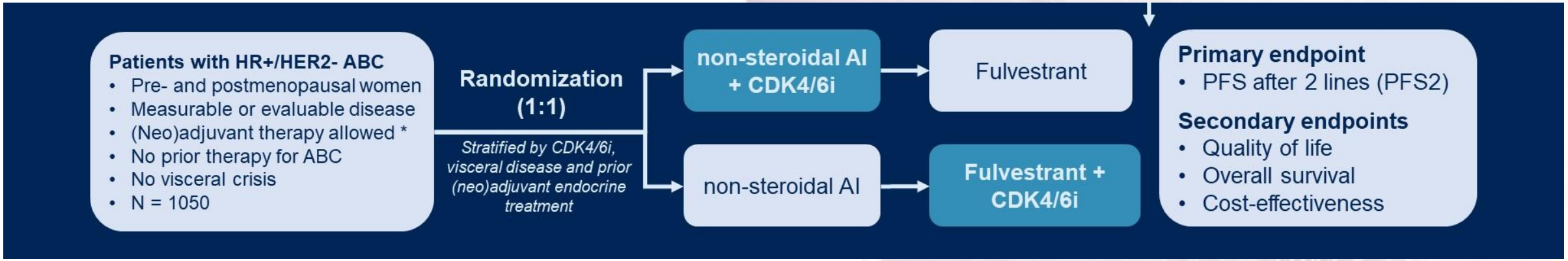
Overall Survival



Qamar Khan, MD. ASCO 2023

SONIA trial

CDK4/6 i: first line vs second line



Inclusion period: November 23, 2017 - September 1, 2021

Data cut-off date: December 1, 2022

Median follow-up: 37.3 months

		First-line CDK4/6i N=524	Second-line CDK4/6i N=526
Patient status, n	First-line treatment ongoing	207	122
	Second-line treatment ongoing	16	82
	Follow-up	117	134
Number of events, n	PFS1	310	407
	PFS2	281	310
	OS	184	188
Median duration on CDK4/6i, months		24.6	8.1

HR+, hormone receptor positive; HER2- , HER2 negative; ABC, advanced breast cancer; AI, aromatase inhibitor; PFS, progression-free survival

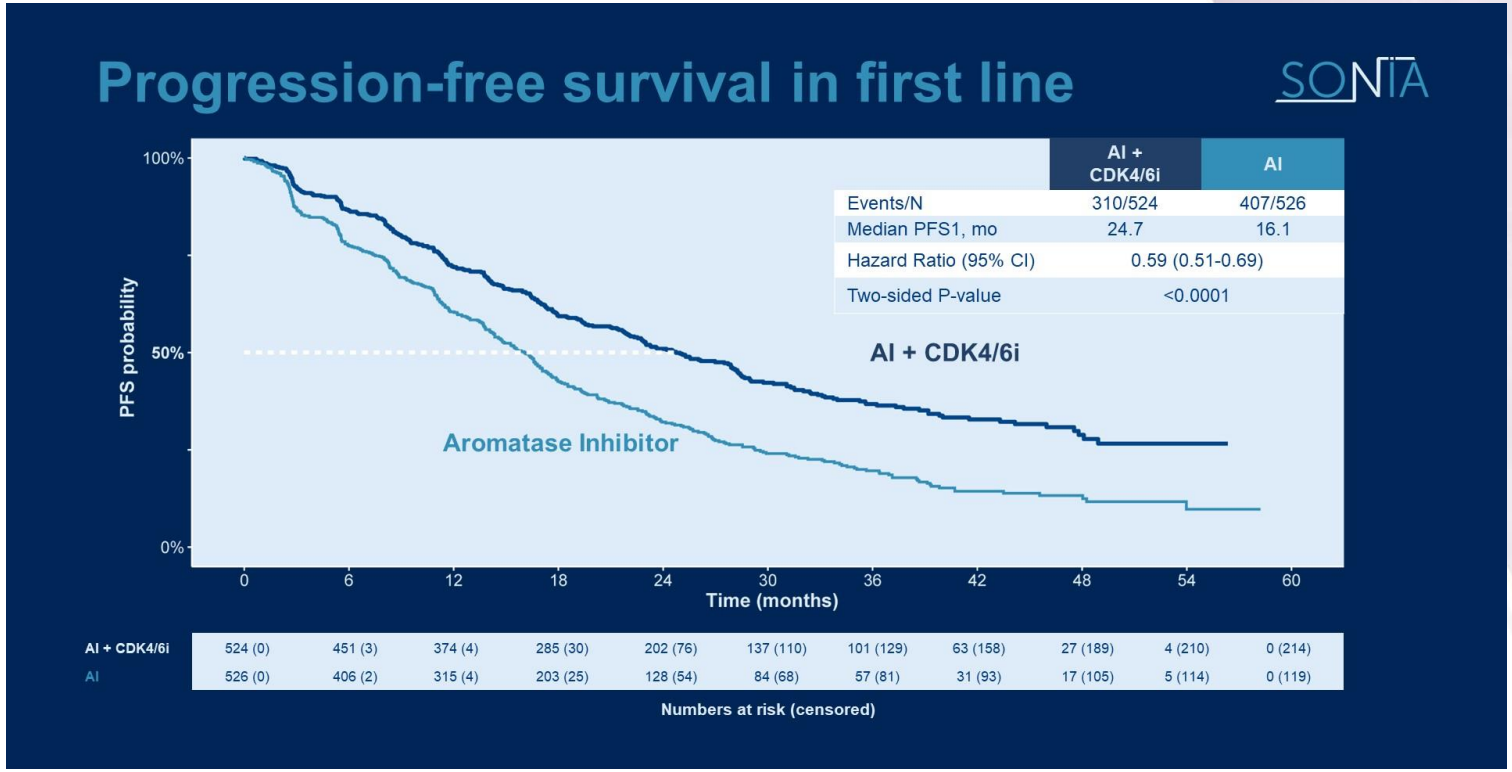
* disease-free interval after non-steroidal aromatase inhibitor >12 months. CllinicalTrials.gov (NCT03425838)

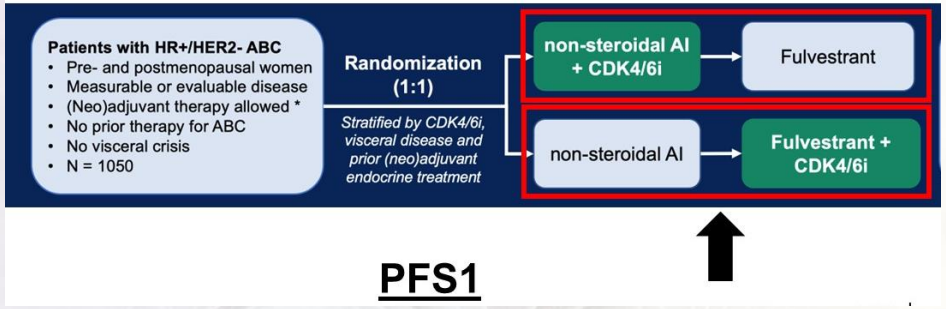
1. Cherny NI, et al. Ann Oncol 2017

Gabe Sonke, ASCO 2023

SONIA trial

CDK4/6 i: first line vs second line





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SONIA trial

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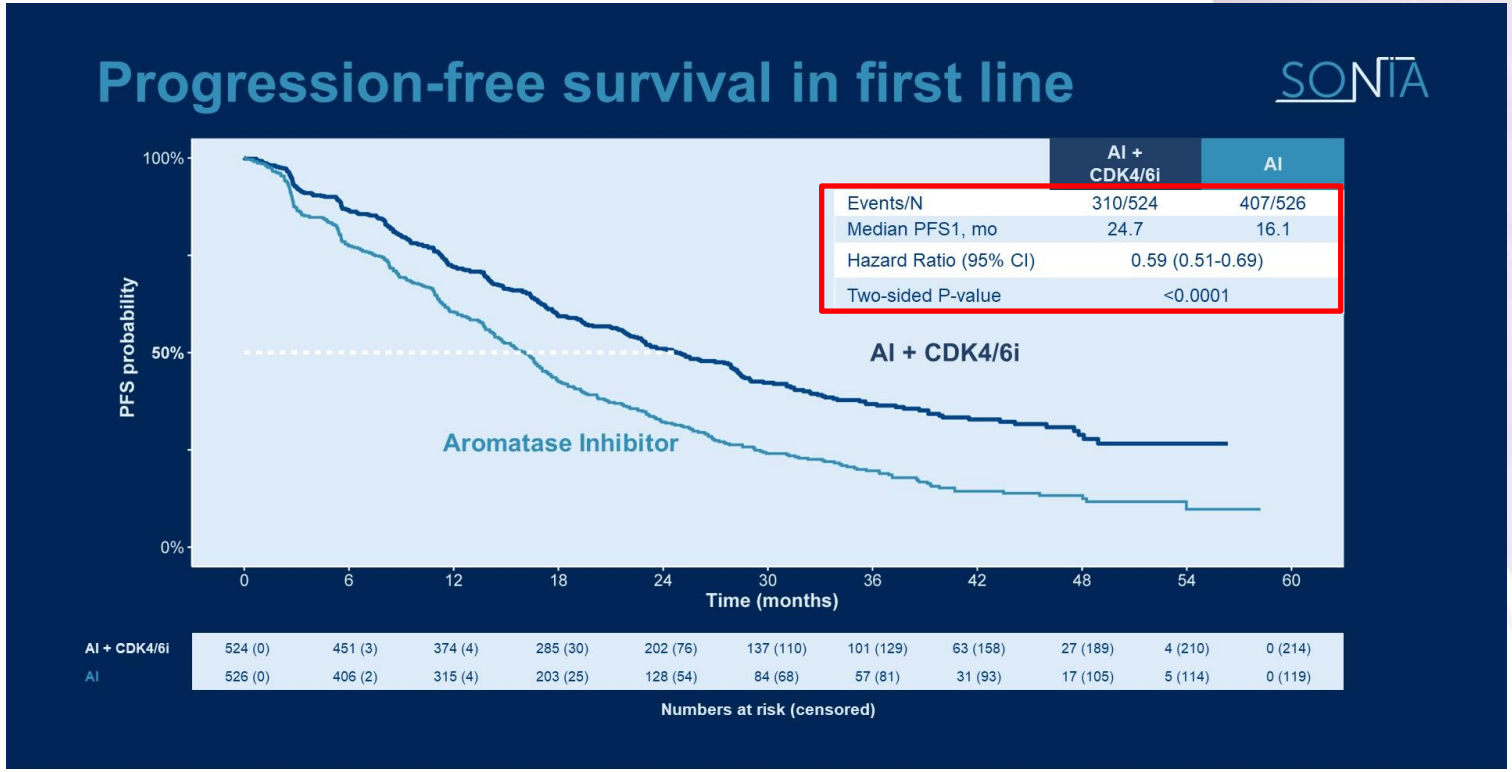

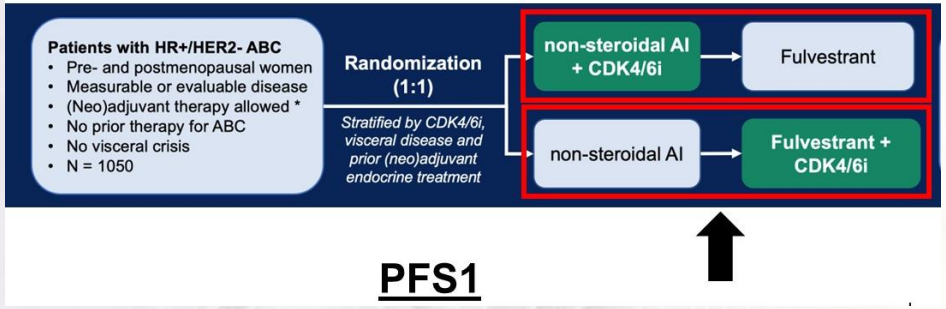

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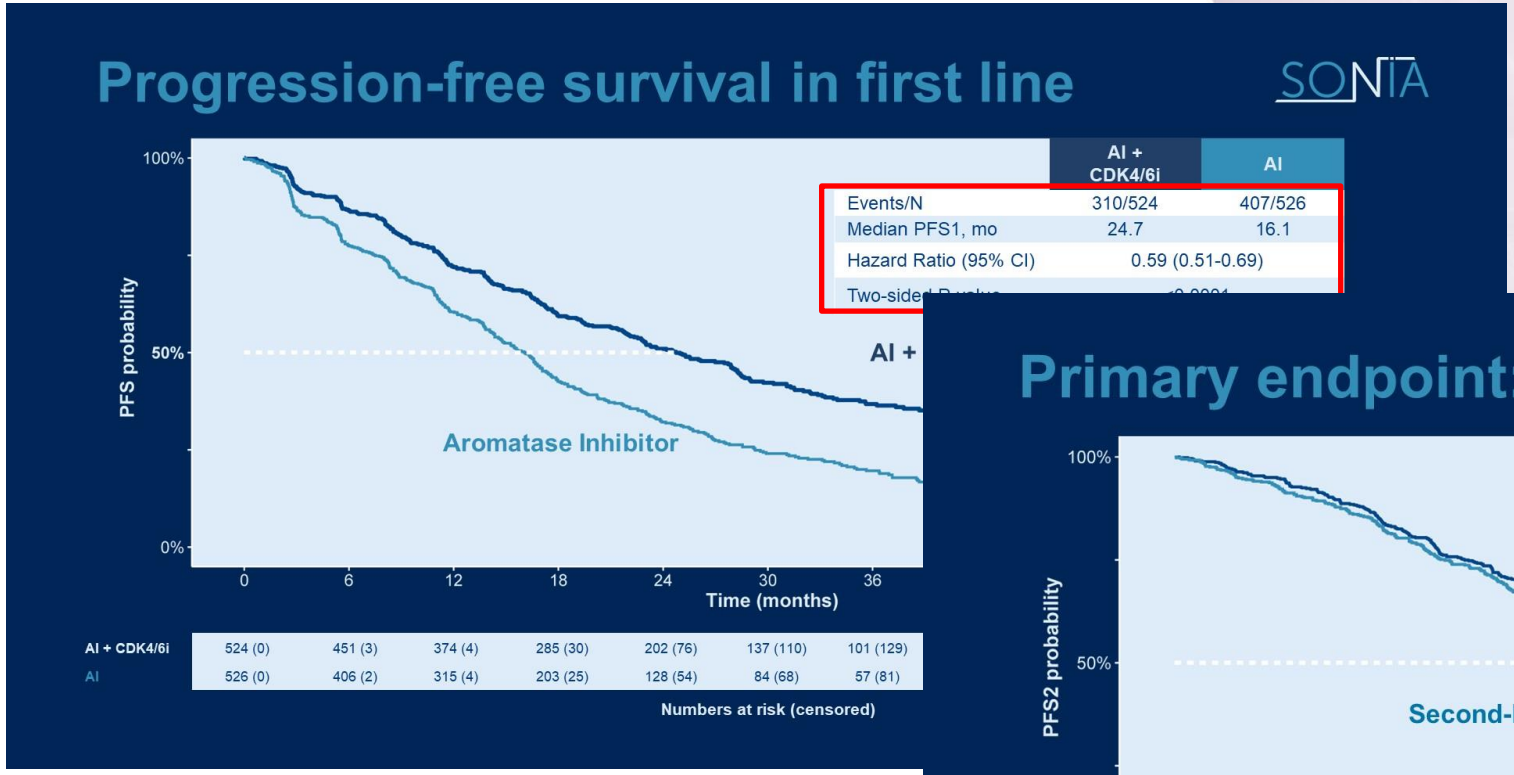
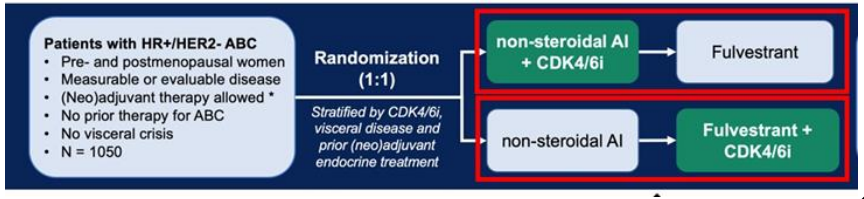
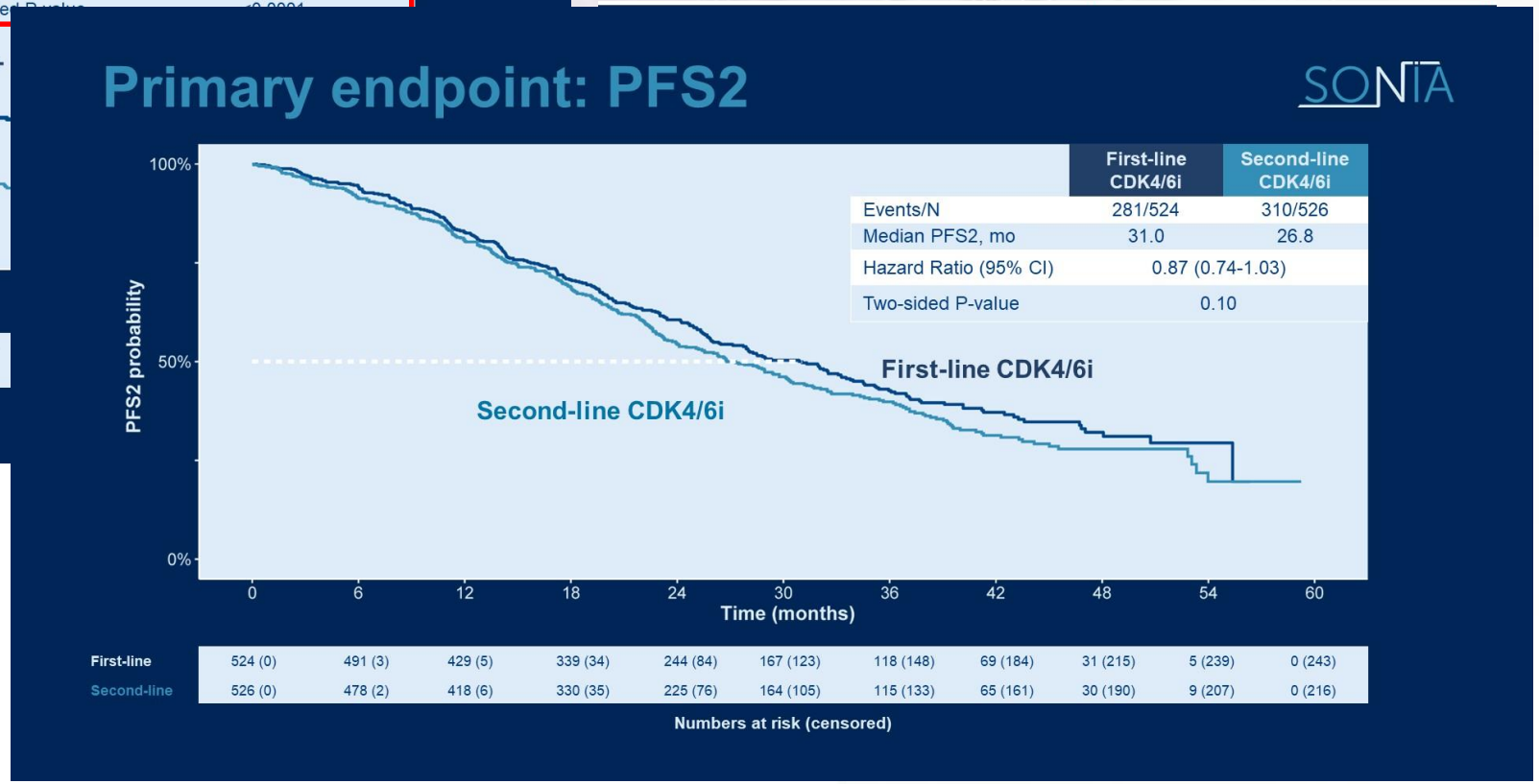
SONIA trial

CDK4/6 i: first line vs second line







PFS 2

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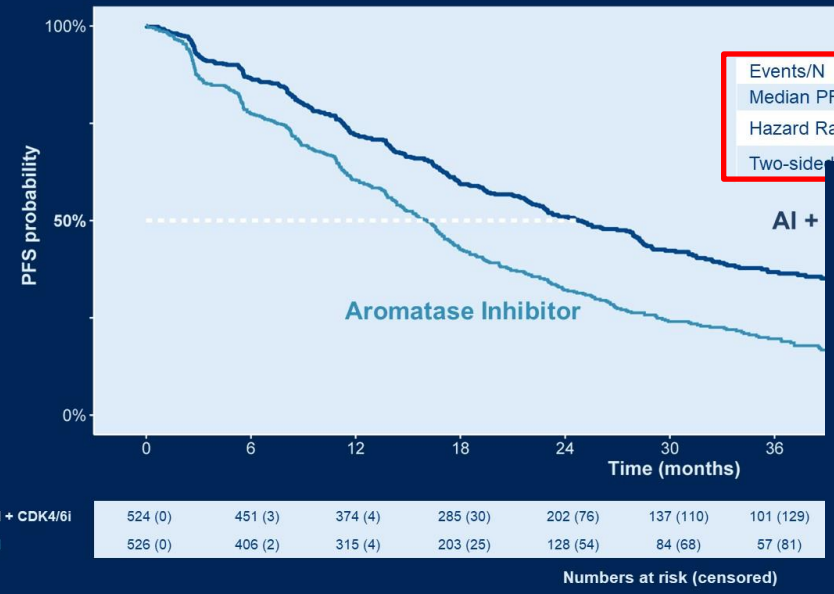
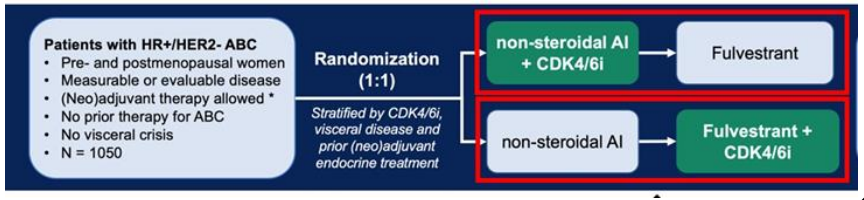
SONIA trial

CDK4/6 i: first line vs second line

Progression-free survival in first line

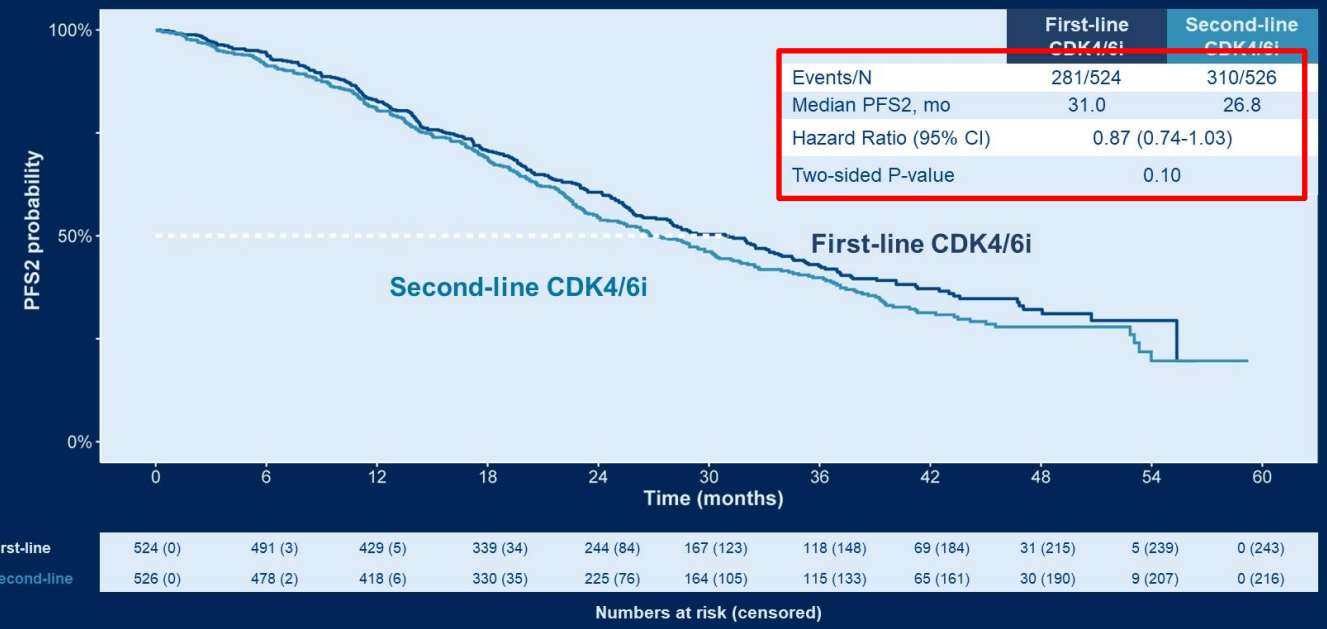


	AI + CDK4/6i	AI
Events/N	310/524	407/526
Median PFS1, mo	24.7	16.1
Hazard Ratio (95% CI)	0.59 (0.51-0.69)	
Two-sided P-value		



PFS 2

Primary endpoint: PFS2



	First-line CDK4/6i	Second-line CDK4/6i
Events/N	281/524	310/526
Median PFS2, mo	31.0	26.8
Hazard Ratio (95% CI)	0.87 (0.74-1.03)	
Two-sided P-value	0.10	

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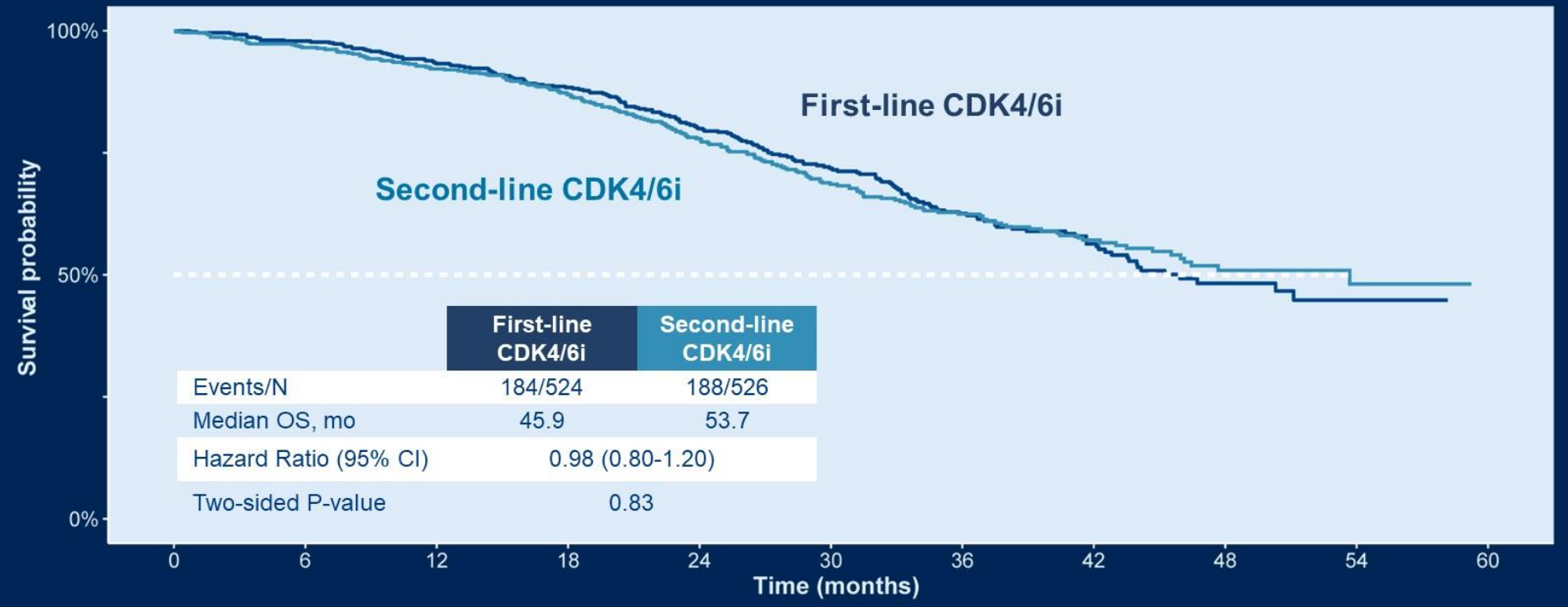
SONIA trial

Overall survival

SONIA



	First-line CDK4/6i	Second-line CDK4/6i
Events/N	184/524	188/526
Median OS, mo	45.9	53.7
Hazard Ratio (95% CI)	0.98 (0.80-1.20)	
Two-sided P-value	0.83	

Numbers at risk (censored)											
First-line	524 (0)	510 (3)	485 (4)	427 (37)	324 (103)	240 (157)	171 (197)	104 (250)	42 (300)	7 (333)	0 (340)
Second-line	526 (0)	506 (2)	483 (2)	426 (32)	328 (89)	242 (139)	175 (186)	112 (236)	52 (287)	16 (322)	0 (338)

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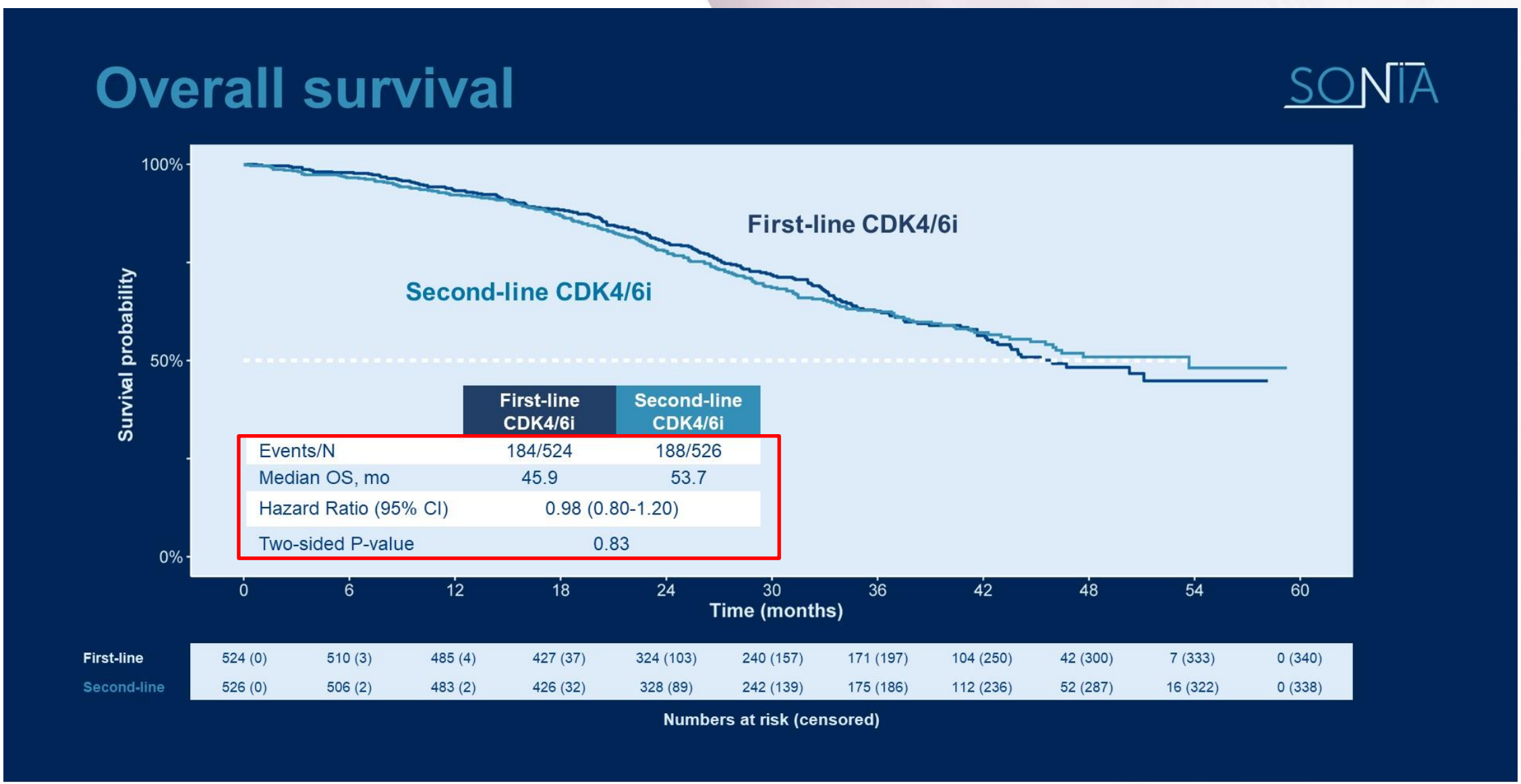
SONIA trial



Gabe Sonke, ASCO 2023

Sonia TRIAL: Summary of the main findings

Summary of the main findings

SONIA

CDK4/6 inhibition in first-line compared to second-line

- Does not improve Progression-Free Survival
- Does not improve Overall Survival
- Does not improve Quality of Life
- Extends time on CDK4/6i by 16.5 months
- Increases incidence of grade 3-4 toxicity by 42%
- Increases drug expenditure by $200,000 per patient[1]

1. CMS drug prices: CMS.gov, Centers for Medicare & Medicaid Services

Gabe Sonke, ASCO 2023

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Gabe Sonke, ASCO 2023

Approach to newly diagnosed HR+/HER2- MBC

Mets identified on imaging

Tumor Biopsy

Receptor status:
-Subtype switch from 1°?
-HER2 low?

Genomic testing to inform 2nd line
-*ESR1? PIK3CA?* TMB? sBRCA?
-Liquid biopsy if tissue fails

First Line Therapy
-Most: ET + ribociclib or abemaciclib
-Select: ET alone | ET+Palbociclib | Chemo | Trial

Definite progression

Liquid biopsy → *ESR1*mut

Second Line Therapy
-PIK3CAmut: Fulvestrant + alpelisib or capivasertib*
***-ESR1*mut**: Elacestrant
-gBRCA1/2 (gPALB2/sBRCA): Olaparib, talazoparib
-No mut: Fulvestrant +/- everolimus or CDK4/6i switch
-Rapid progression: Chemotherapy/ADC*

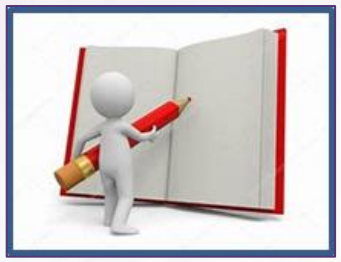
Indeterminate progression

?Repeat genomic testing:
-Liquid biopsy → *ESR1*mut

Consider ET switch:
AI→Fulvestrant

Dr. Daniel Stover, ASCO 2023

Take-home messages



- Consolidated data of CDK4/6i in 1st and 2nd line of Luminal MBC.
  - Differences between CDK4/6i → Customize treatment?
  - Should all patients receive CDK4/6 inhibitors in the first line? → SONIA.
  - Early switch: ESR1 mut ctDNA → PADA-1.

- To the progression CDK4/6i:
  - Fulvestrant monotherapy → Probably not optimal treatment.
  - Rechallenge with CDK4/6i → PACE: negative. MAINTAIN: positive.
  - Maintain CDK4/6i and change endocrinal treatment → PALMIRA: negative.
  - PIK3CA/AKT mut → Alpelisib (BYLive, SOLAR1), Capivasertib (CAPITELLO).
  - ESR1 mut → Elacestrant (EMERALD), Camizestrant (SERENA-2).

Take-home messages

- The importance of "academic research".
- More options of treatments in luminal metastatic breast cancer

  $\rightarrow \uparrow$ PFS and OS $\rightarrow$ Sort, prioritize.
- What we do after CDK4/6i in adjuvancy?
- I haven't talked about HER 2 low..... (Dra. Echavarría).

Thanks to Dr. Stover and Dr. Sonke for authorizing slides

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