



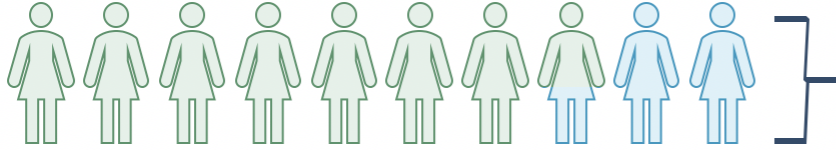
18^{as} Jornadas HITOS
ONCOLÓGICOS: LO MEJOR DE **2023**

Madrid, 22 y 23 de noviembre de 2023

Treatment sequencing in ER+ HER2- ABC

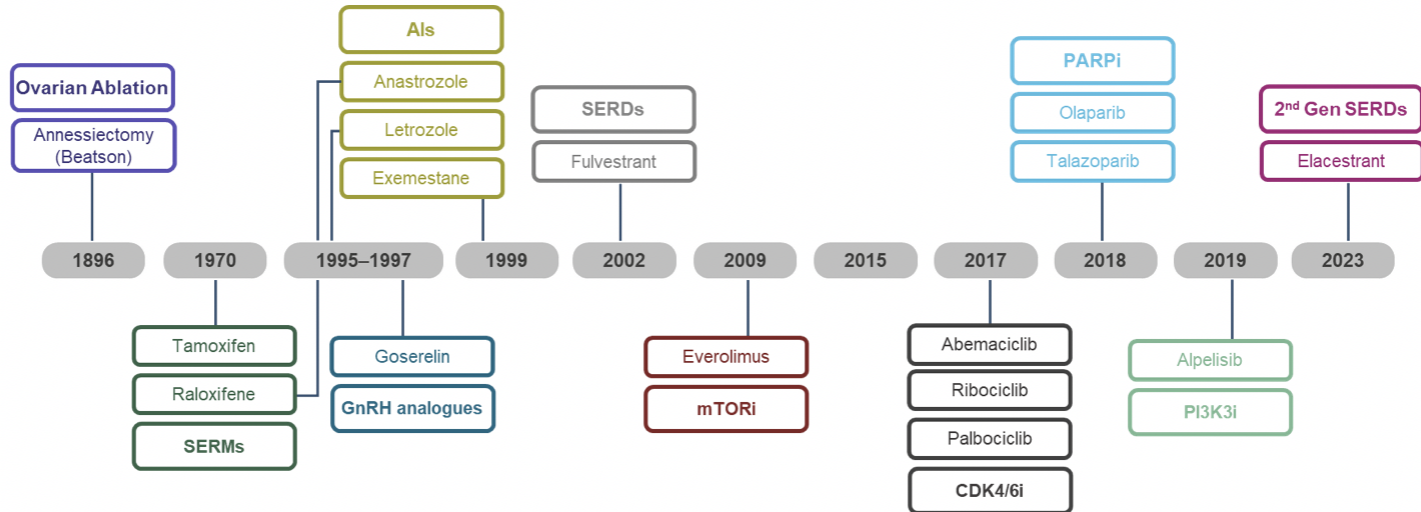
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Medical Oncology Dpt
Hospital 12 de Octubre
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Grupo SOLTI

- HR+/HER2- mBC is the most common subtype of breast cancer¹



~75% of patients with breast cancer are HR+/HER2-

Targeted therapy for HR+ BC: Evolving landscape^{2,3}



- Progression-free and overall survival data

	PALOMA-2	MONALEESA-2	MONARCH-3
Phase	Phase 3	Phase 3	Phase 3
Line	1 st line	1 st line	1 st 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

Summary of CDK4/6i Data

HR+/HER2- Endocrine-sensitive MBC

First-line (*de novo*
MBC or DFI>12
months from ET
for EBC)

PALOMA 2

Postmenopausal
HR+/HER2- BC
No previous
treatment for ABC
N = 666

(R)

Palbociclib
+ letrozole
Placebo
+ letrozole

MONALEESA 2

Postmenopausal
HR+/HER2- BC
No previous
treatment for ABC
N = 668

(R)

Ribociclib
+ letrozole
Placebo
+ letrozole

MONARCH 3

Postmenopausal
HR+/HER2- BC
No previous
treatment for ABC
N = 493

(R)

Abemaciclib
+ NSA
Placebo
+ NSA

MONALEESA 7

Premenopausal
HR+/HER2- BC
No previous
endocrine
treatment for ABC
N = 672

(R)

Ribociclib
+ AI/Tam (+ OFS)
Placebo
+ AI/Tam (+ OFS)

MONALEESA 3

HR+/HER2- MBC
PD after ET for MBC
or DFI ≤12 months
after ET for EBC
N = 484

(R)

Ribociclib
+ fulvestrant
Placebo
+ fulvestrant

PALOMA 3

HR+/HER2- MBC
PD after ET for MBC
or DFI ≤12 months
after ET for EBC
N = 521

(R)

Palbociclib
+ fulvestrant
Placebo
+ fulvestrant

MONARCH 2

Postmenopausal
HR+/HER2- MBC
PD after ET for MBC
or DFI ≤12 months
after ET for EBC
N = 669

(R)

Abemaciclib
+ fulvestrant
Placebo
+ fulvestrant

HR+/HER2- Endocrine-resistant MBC

Second-line or
first-line with DFI≤12
months from ET for
EBC

PFS data



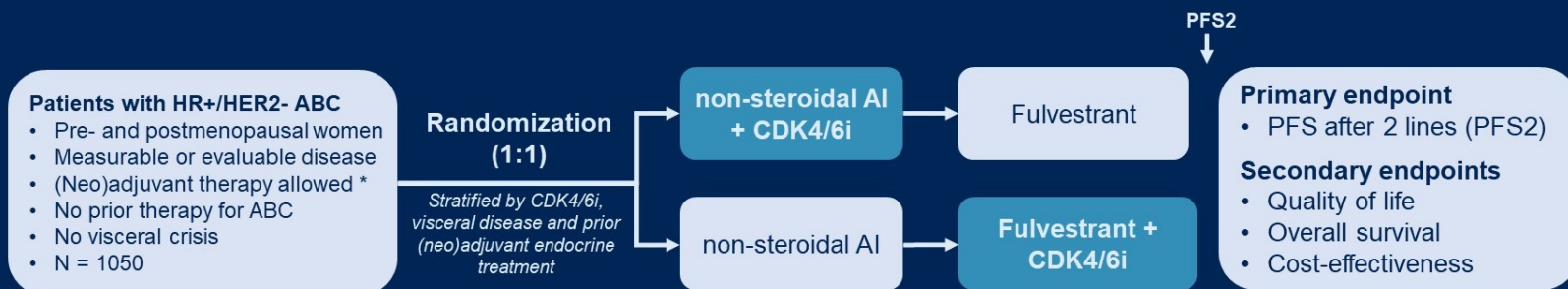
OS data



When to use CDKi?

SONIA trial design

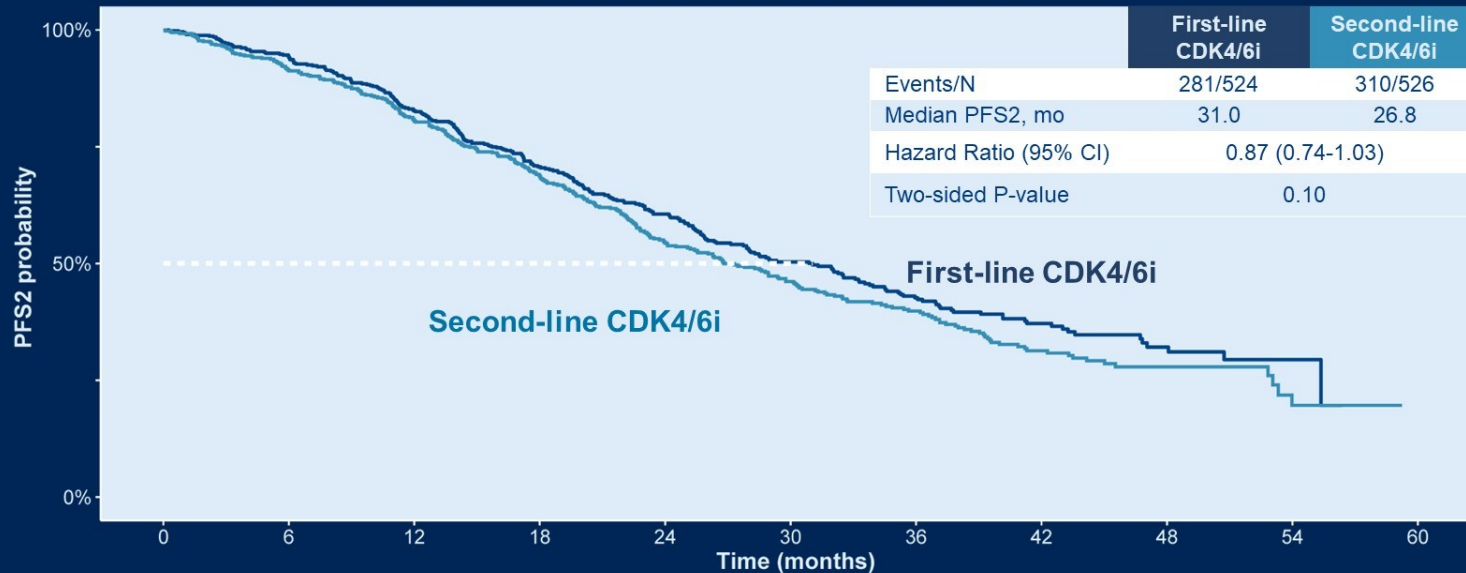
SONIA



- Tumor assessments every 12 weeks
- PFS locally assessed per RECIST v1.1
- Primary analysis planned after 574 PFS2 events
 - 89% power to detect superiority according to ESMO MCBS (HR lower limit CI ≤ 0.65 and $\Delta \geq 3$ months) with two-sided $\alpha=5\%$ ¹

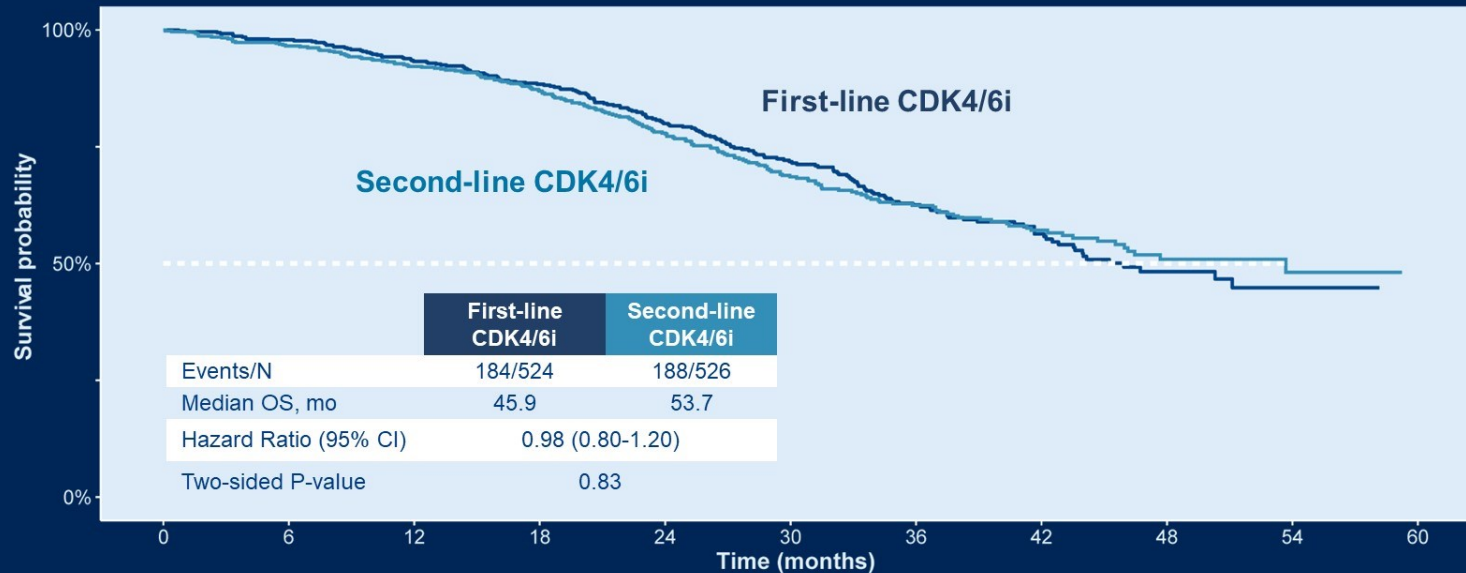
HR+, hormone receptor positive; HER2-, HER2 negative; ABC, advanced breast cancer; AI, aromatase inhibitor; PFS, progression-free survival
* disease-free interval after non-steroidal aromatase inhibitor >12 months. ClinicalTrials.gov (NCT03425838)
1. Cherny NI, et al. Ann Oncol 2017

Primary endpoint: PFS2



First-line	524 (0)	491 (3)	429 (5)	339 (34)	244 (84)	167 (123)	118 (148)	69 (184)	31 (215)	5 (239)	0 (243)
Second-line	526 (0)	478 (2)	418 (6)	330 (35)	225 (76)	164 (105)	115 (133)	65 (161)	30 (190)	9 (207)	0 (216)
Numbers at risk (censored)											

Overall survival



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)
Numbers at risk (censored)											

1st Line: RIGHT Choice

Primary analysis (NCT03839823)

Study design:
Randomised, open-label, Phase 2 trial

Pre-/perimenopausal women
HR+/ HER2- ABC (>10% ER+)
No prior systemic therapy for ABC
N=222

R
1:1

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

Investigators' choice of
combination CT
Docetaxel + capecitabine
Paclitaxel + gemcitabine
Capecitabine + vinorelbine

Primary endpoint: PFS

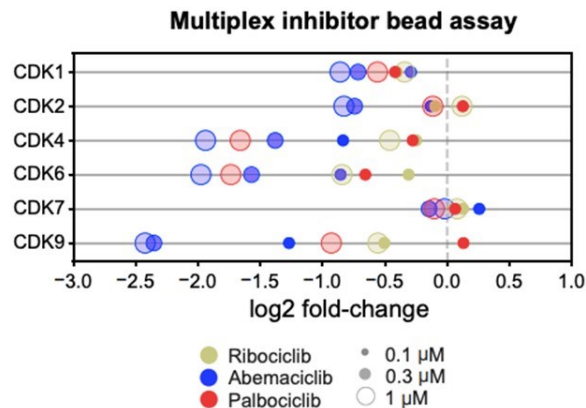
	RIB + ET (n=112)	Combo CT (n=110) ^a
Events, %	52	58
Median PFS, months	24.0	12.3
Hazard ratio (95% CI)	0.54 (0.36–0.79)	
p-value	0.0007	

Safety summary

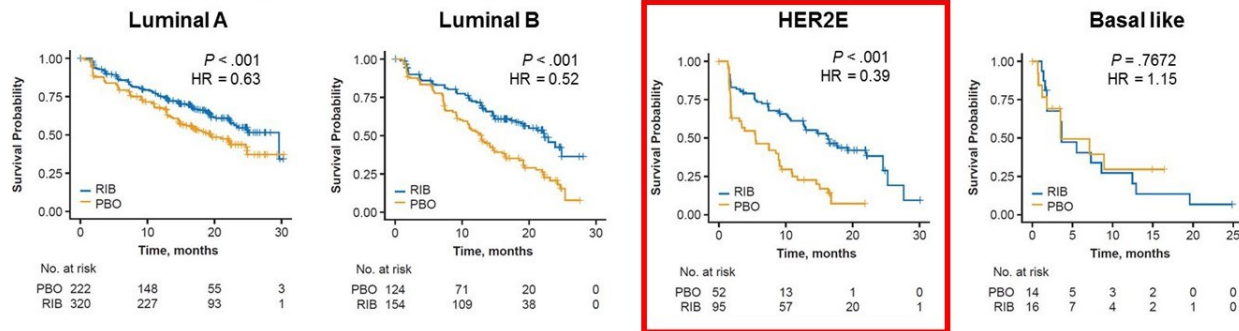
n (%)	RIB + ET (n=112)		Combo CT (n=110) ^a	
	All grade	Grade 3/4	All grade	Grade 3/4
Total AEs,	112 (100.0)	84 (75.0)	100 (100.0)	71 (71.0)
Treatment-related serious AEs	2 (1.8)	1 (0.9)	8 (8.0)	7 (7.0)
TRAE leading to discontinuation ^b	8 (7.1)	7 (6.3)	23 (23.0)	7 (7.0)

Can we choose the best CDKi for each
pt?

- Progression-free and overall survival data
- CDK4/6 inhibitors are not identical pharmacologically
 - Ribociclib CDK4>CDK6, Abemaciclib CDK1,CDK2
- Differences by molecular subtype?
 - MONALEESA studies:



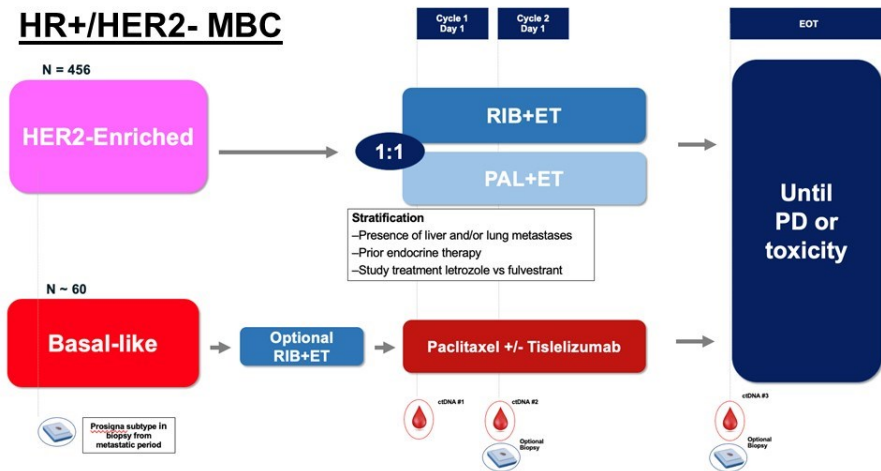
Hafner *Cell Chem Bio* 2019



Prat *JCO* 2021

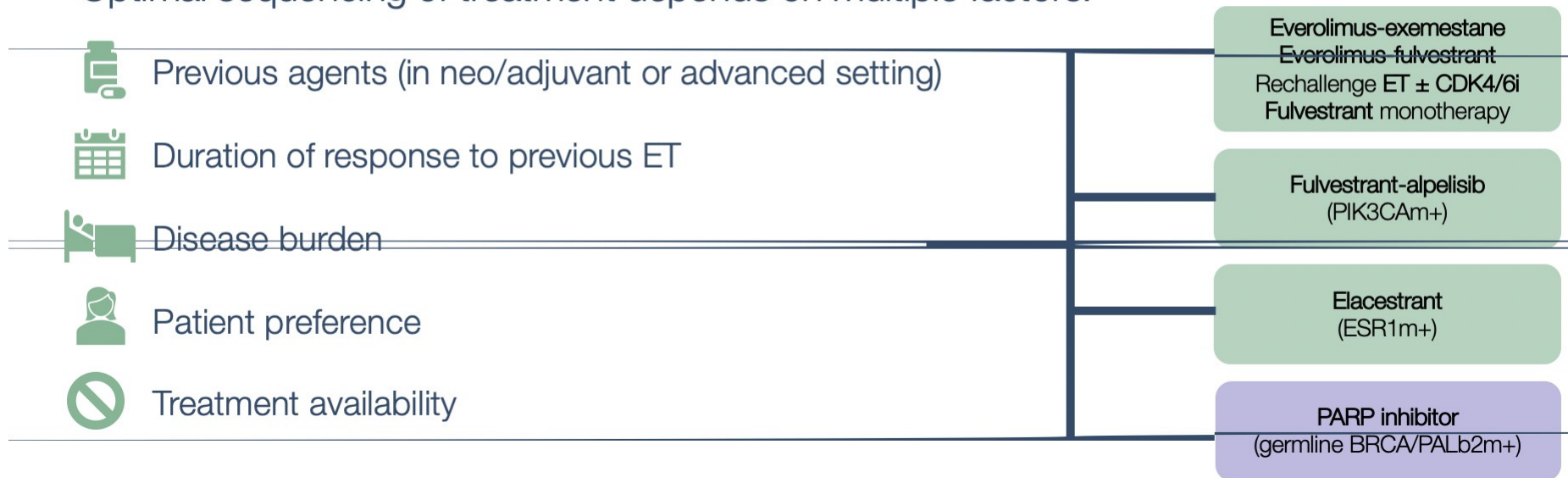
- Progression-free and overall survival data
- CDK4/6 inhibitors are not identical pharmacologically
 - Ribociclib CDK4>CDK6, Abemaciclib CDK1,CDK2
- Differences by molecular subtype?
 - MONALEESA studies
 - **HARMONIA** (SOLTI-2101 / AFT-58)

Increasingly, data suggest that CDK4/6 inhibitors are not interchangeable



After CDKi progression

- There are multiple options after progression on CDK4/6 inhibitors
- Optimal sequencing of treatment depends on multiple factors:



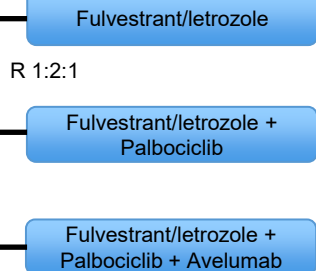
Endocrine therapy switch – maintaining CDKi

Studies Assessing CDK4 & 6 Inhibitor Sequencing in HR+, HER2- ABC

PACE (NCT03147287)¹

n=220

- Men and pre- and post-menopausal women
- Progression on and response to prior CDK4 & 6i in adjuvant or metastatic (ET partner: only AI or tam) setting
- Metastatic setting: 0-1 lines prior chemo, 1-2 lines prior ET
- 1 intervening line of therapy allowed after CDK4 & 6i

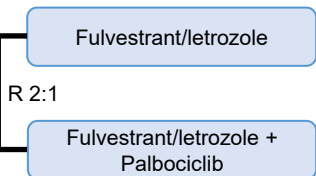


Primary PFS

PALMIRA (NCT03809988)³

n=198

- Pre- and post-menopausal women
- Progression on and response to Palbociclib plus AI or fulvestrant (no tam)
- Metastatic setting: Not treated with at least 1 ET option: AI or fulvestrant
- No other systemic therapy for metastatic disease

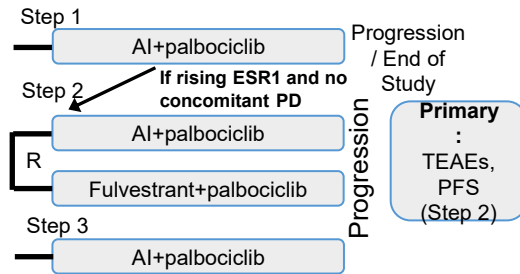


Primary PFS

PADA-1 (NCT03079011)²

n=1017

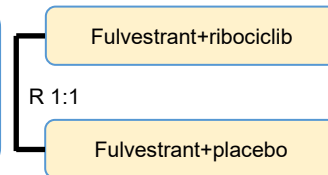
- Pre- and post-menopausal women
- No prior systemic anti-cancer therapy for metastatic disease
- No prior ET in the metastatic setting
- No prior CDK4 & 6i in the adjuvant or metastatic setting



MAINTAIN (NCT02632045)⁴

n=132

- Men and pre- and post-menopausal women
- Progression on and response to any CDK4 & 6i plus AI



Primary Percent PFS at 24 weeks

¹ Mayer et al. 2018 JCO 36(15) TPS 1104

² Bidard et al. 2020 JCO 38: 2020 (suppl; abstr 1010)

³ Lombart Cussac et al. ESMO 2019 30 (suppl_5): v104-v142 Abs3516

⁴ Kalinsky et al. 2017 JCO 35(15) TPS 1112

See notes section for abbreviations

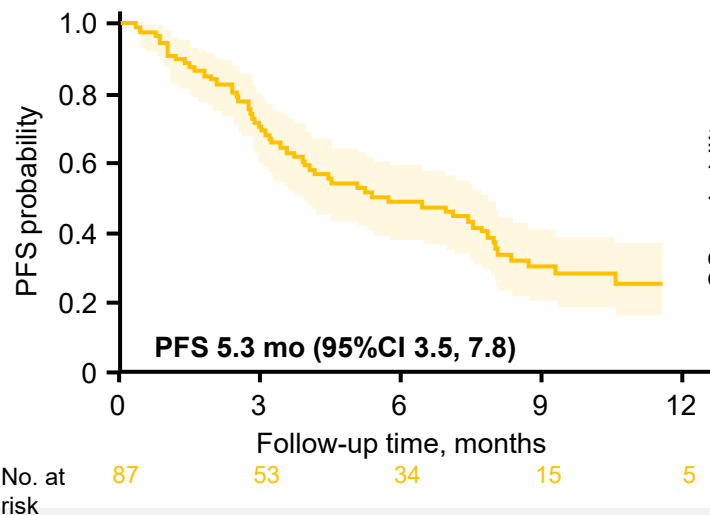
	MAINTAIN	PACE	PALMIRA
Patients (n)	120	166	198
1 st line CDK4/6i	Palbociclib (84%)	Palbociclib (90%)	Palbociclib (100%)
% 1 st line CDK4/6i >12mo	67%	75%	86%
Endocrine therapy	Fulvestrant (83%) or exemestane	Fulvestrant (100%)	Fulvestrant (90%) or letrozole
'Continuation' CDK4/6i	Ribociclib	Palbociclib	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

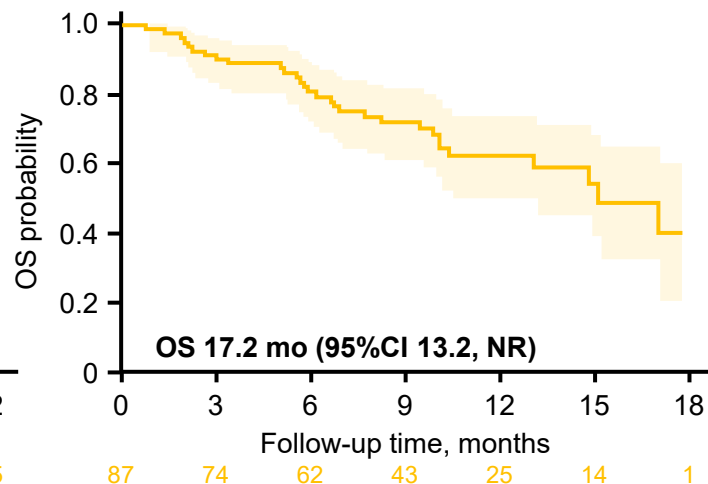
Kalinsky JCO 2023; Mayer SABCS 2022; Llombart-Cussac ASCO 2023

Clinical outcomes with abemaciclib after prior CDK4/6 inhibitor progression

Progression-free survival



Overall survival



Safety

- Abemaciclib was generally well-tolerated after a prior course of CDK4/6 inhibitor therapy with only 8 (9.2%) patients discontinuing because of toxicity without progression

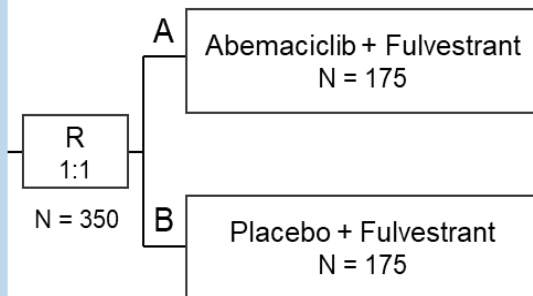
Conclusions

- In heavily pre-treated patients with HR+ MBC, abemaciclib demonstrated durable clinical benefit in a subgroup (36.8%) who experienced progression on palbociclib and was generally well-tolerated

postMONARCH Study Design

Key Inclusion Criteria:

- HR+, HER2- advanced or metastatic breast cancer
- Men or pre-/post-menopausal women
- Prior therapy:
 - Advanced setting: Disease progression on CDK4 & 6 inhibitor plus AI as initial therapy, **OR**
 - Adjuvant setting: Disease recurrence on or after CDK4 & 6 inhibitor plus ET



Primary Endpoint:
Investigator-assessed PFS

Secondary Endpoints:
OS, PFS by BICR, ORR, CBR, DCR,
DoR, Safety, PRO, PK

Stratification factors:

- Geography: USA, East Asia, or other (including EU)
- Presence of visceral metastases: yes or no
- Duration on prior CDK4 & 6 inhibitor-based regimen:
 - <12 months if prior treatment was in metastatic setting; or disease recurrence during CDK4 & 6 inhibitor-based regimen if treated in adjuvant setting; OR
 - ≥12 months if prior treatment was in metastatic setting; or disease recurrence after completing CDK4 & 6 inhibitor-based regimen if treated in adjuvant setting

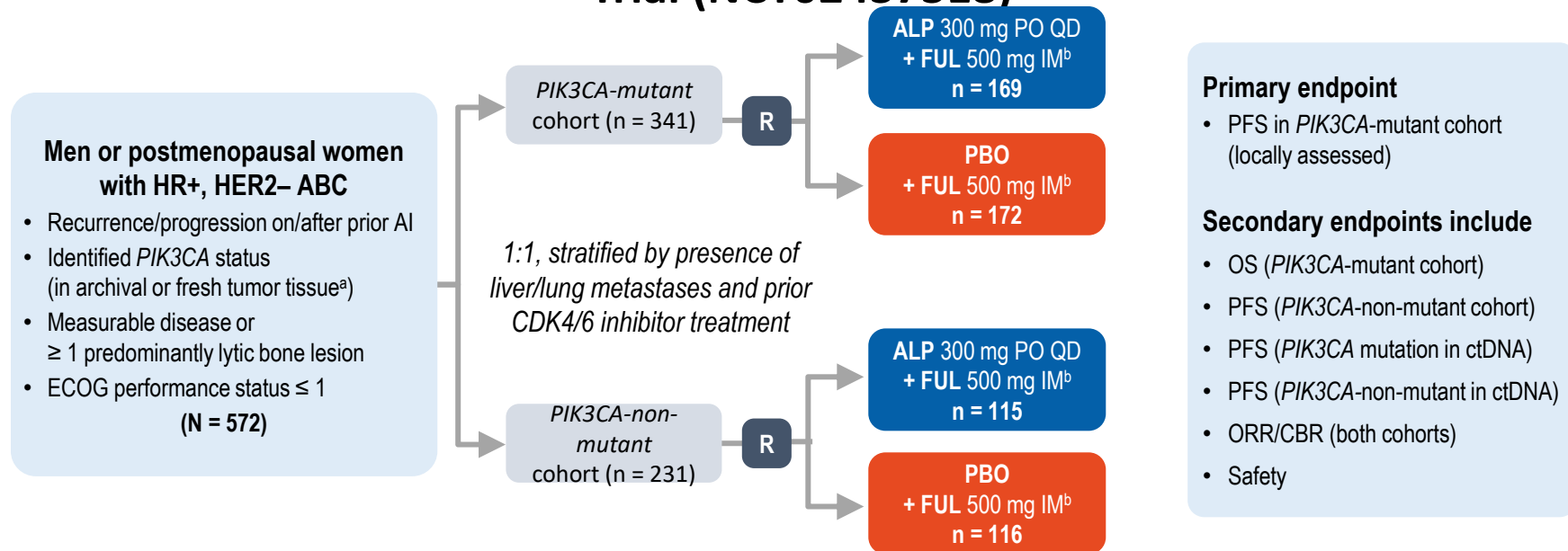
AI: aromatase inhibitor
BICR: blinded independent central review
CBR: clinical benefit rate
CDK4 & 6: cyclin-dependent kinase 4 & 6
DCR: disease control rate
DoR: duration of response
ET: endocrine therapy

HR: hormone receptor
HER2: human epidermal growth factor receptor 2
OS: overall survival
PFS: progression free survival
ORR: objective response rate
PK: pharmacokinetics
PRO: patient reported outcomes

PIK3CA / AKT / mTOR pathway

PIK3CA / AKT / mTOR pathway

SOLAR-1: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial (NCT02437318)¹



- The primary endpoint included all randomized patients in the *PIK3CA*-mutant cohort; PFS was analyzed in the *PIK3CA*-non-mutant cohort as a proof of concept
- Safety was analyzed for all patients who received ≥ 1 dose of study treatment, in both cohorts

ABC, advanced breast cancer; AI, aromatase inhibitor; ALP, alpelisib; CBR, clinical benefit rate; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; FUL, fulvestrant; HER2-, human epidermal growth factor receptor-2-negative; IM, intramuscular; ORR, overall response rate; OS, overall survival; PBO, placebo; PFS, progression-free survival; PO, oral; QD, once daily; R, randomization.

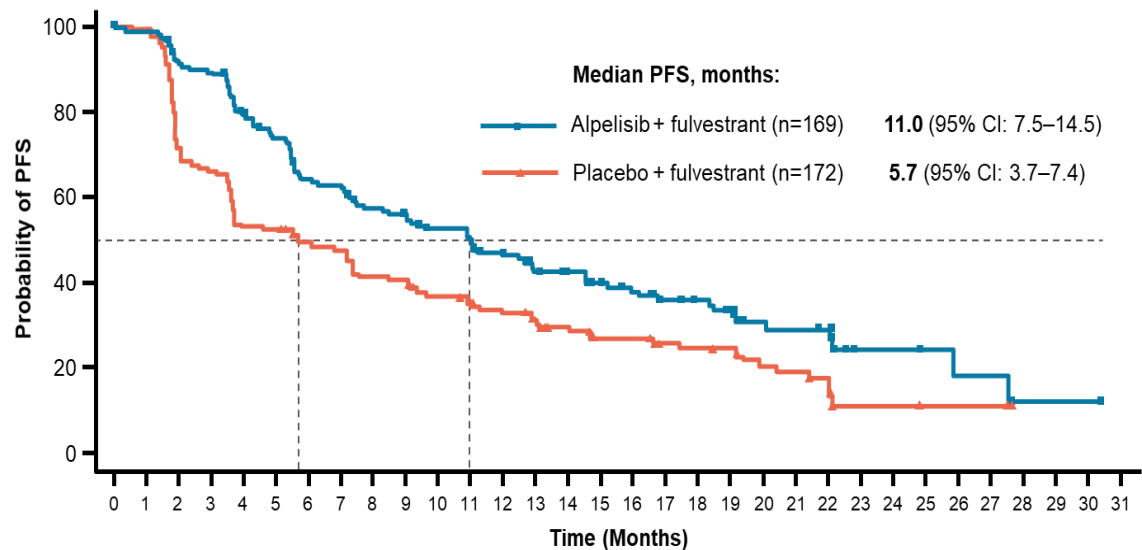
^a More than 90% of patients had mutational status identified from archival tissue.

^b Fulvestrant given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of subsequent 28-day cycles.

1. Andre F, et al. ESMO 2018. Abstract LBA3 [oral].

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Primary Endpoint: Locally Assessed PFS in the *PIK3CA*-mutant Cohort^{1,a}



Data cut-off: Jun 12, 2018	ALP + FUL (n = 169)	PBO + FUL (n = 172)
Number of PFS events, n (%)	103 (60.9)	129 (75.0)
Progression	99 (58.6)	120 (69.8)
Death	4 (2.4)	9 (5.2)
Censored	66 (39.1)	43 (25.0)
Median PFS (95% CI)	11.0 (7.5-14.5)	5.7 (3.7-7.4)
HR (95% CI)	0.65 (0.50-0.85)	
One-sided P value	0.00065	

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

At final PFS analysis, superiority was declared if one-sided, stratified log-rank test P value was ≤ 0.0199 (Haybittle–Peto boundary).

^a Mutation status determined from tissue biopsy.

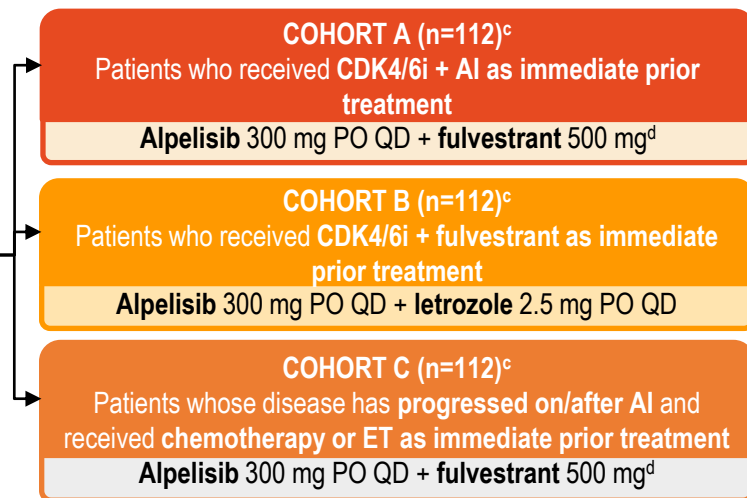
1. Andre F, et al. ESMO 2018. Abstract LBA3 [oral].

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BYLieve Study (CBYL719X2402)

Phase II, open-label, three-cohort, noncomparative study to assess the efficacy and safety of alpelisib + ET (fulvestrant or letrozole) in patients with *PIK3CA*-mutated, HR+ HER2— ABC whose disease progressed on/after prior treatments

- Men or pre/postmenopausal^a women with HR+, HER2—, *PIK3CA*-mutated ABC
 - *PIK3CA* mutation in tumor tissue or blood^b
 - Last line of prior therapy: CDK4/6i + ET, systemic chemotherapy, or ET
 - ECOG PS ≤2
 - Measurable disease (per RECIST v1.1) or ≥1 predominantly lytic bone lesion
- (N=336)^c



Primary endpoint

- Proportion of patients alive without PD at 6 months (RECIST v1.1) in each cohort

Secondary endpoints

- PFS
- PFS2
- ORR, CBR, DOR
- OS
- Safety

Exploratory endpoint

- Biomarker analyses

Treatment crossover between cohorts not permitted

^aMen (Cohort B only) and premenopausal women were allowed goserelin 3.6 mg SC every 28 days or leuprolide 7.5 mg IM every 28 days for adequate gonadal suppression; ^bPatients were enrolled and could stay on study based on confirmed *PIK3CA* mutation status from either tissue or blood by a certified local laboratory. Only patients with centrally confirmed *PIK3CA* mutation by a Novartis-designated laboratory were included in the mFAS; ^cEnrollment continued until 336 patients with a centrally confirmed *PIK3CA* mutation was reached (at least 112 patients in each cohort); ^dIM on D1 and D15 of Cycle 1 and D1 for all other cycles thereafter.

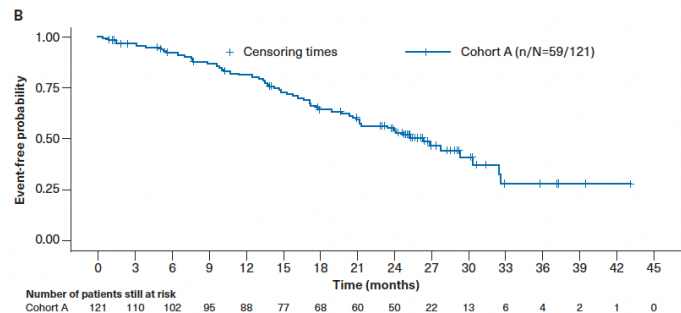
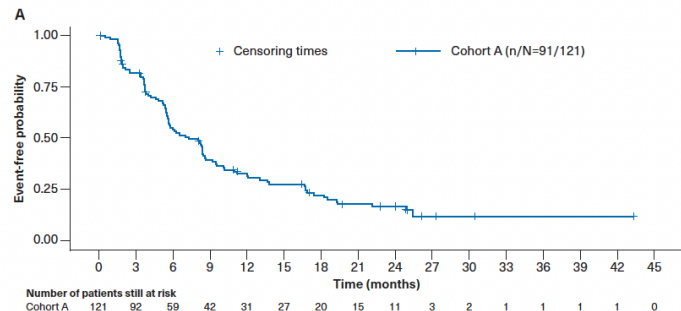
ABC, advanced breast cancer; AI, aromatase inhibitor; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; D, Day; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2—, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; IM, intramuscular; mFAS, modified Full Analysis Set; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, second progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PO, orally; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; SC, subcutaneously.

mFU 18m Cohort A

18-Month Efficacy Outcomes

- At 18-months' follow-up, median PFS was 7.3 mo (95% CI, 5.6-8.5 mo); the percentage of patients with PFS at 18 months was 22.2% (95% CI, 14.8%-30.7%; **Figure 2A**)
- At 18-months' follow-up, median OS was 26.4 mo (95% CI 21.0-30.5 mo), and 18-month OS was 65.3% (95% CI, 55.6%-73.4%; **Figure 2B**)

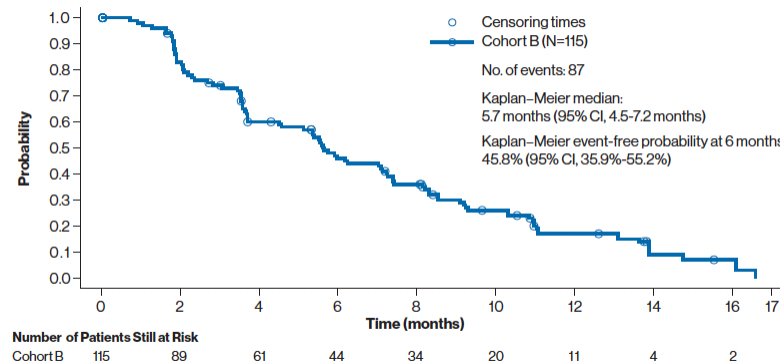
Figure 2. Progression-Free Survival, 18-Month Follow-up (A); Overall Survival, 18-Month Follow-up (B)



Cohort A: Alpelisib + fulvestrant.
Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982). % Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point.
Event-free probability estimates are obtained from the Kaplan-Meier survival estimates for all treatment groups; Greenwood formula is used for CIs of Kaplan-Meier estimates.
n: Total number of events included in the analysis.
N: Total number of patients included in the analysis.

- Median PFS on the next line of therapy (PFS2) was 15.9 months (95% CI, 12.1-21.7 mo) (**Figure 3**)
- The percentage of patients with PFS on the next line of therapy at 18 months was 46.5% (95% CI, 36.9%-55.5%)

Figure 3. Kaplan-Meier Plot of Time to PFS per Local Investigator Assessment



Cohort B

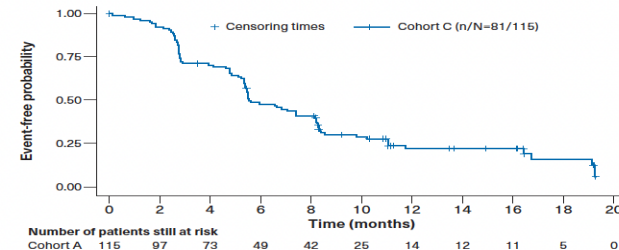
Table 3. Efficacy of Alpelisib + Fulvestrant per Local Investigator Assessment

Primary Endpoint	Cohort C, Prior Chemotherapy or ET (N=115)
Proportion of patients who were alive without disease progression at 6 months as assessed by local investigator, %	48.7 (n=56; 95% CI, 39.27-58.19)
ET, endocrine therapy.	

- mPFS was 5.6 months (95% CI, 5.4-8.1 mo; **Figure 3**); mPFS by prior therapy in metastatic/adjunct setting is presented on **Table 4**

Cohort C

Figure 3. Kaplan-Meier Plot of Time to PFS per Local Investigator Assessment



CI, confidence interval; mPFS, median progression-free survival.

PIK3CA / AKT / mTOR pathway

CAPItello-291 Study Design

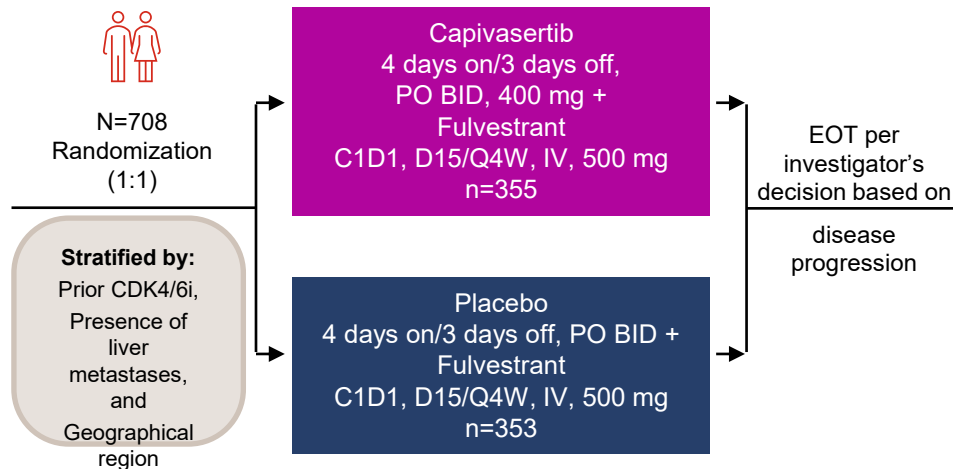
Objective: To analyze the efficacy and safety of administering capivasertib in combination with fulvestrant versus placebo + fulvestrant in patients with HR+, HER2- locally advanced (inoperable) or metastatic breast cancer

Inclusion criteria:

- ◆ Pre-/postmenopausal women and men with HR+, HER2- ABC
- ◆ PD with prior AI^a or recurrence at ≤12 months of EOT with adjuvant AI
- ◆ ET (≤2 lines) and CT (≤1 line)^a
- ◆ Availability of FFPE sample from primary/recurrent tumor
- ◆ Prior exposure to CDK4/6i^b allowed

Exclusion criteria:

- ◆ Prior SERD, mTORi, PI3Ki, or AKTi
- ◆ HbA1c ≥8.0% and diabetes requiring insulin



Primary endpoint:

- ◆ Investigator-assessed progression-free survival
 - Overall population
 - Patients with AKT pathway-altered tumors (≥1 alteration in *PIK3CA*, *AKT1*, or *PTEN*)

Secondary endpoints:

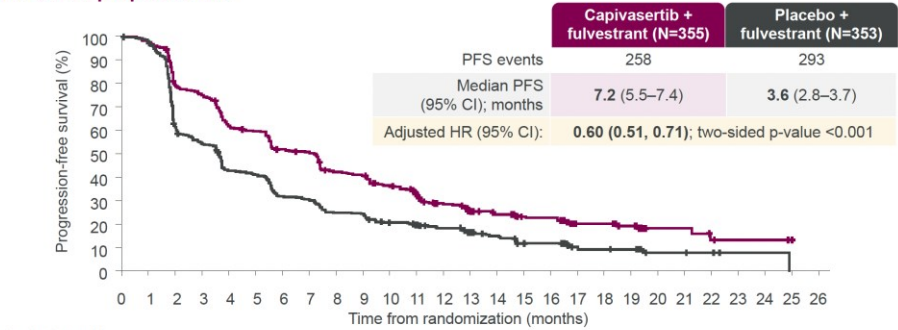
- ◆ Overall survival
 - Overall population
 - AKT-pathway tumor population
- ◆ Overall response rate
 - Overall population
 - AKT-pathway tumor population

^aIn the ABC setting; ^bRequirement of ≥51%.

Full list of abbreviations available in the speaker notes.

Turner NC, et al. Presented at: SABCS 2022. Abstract GS3-04.

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



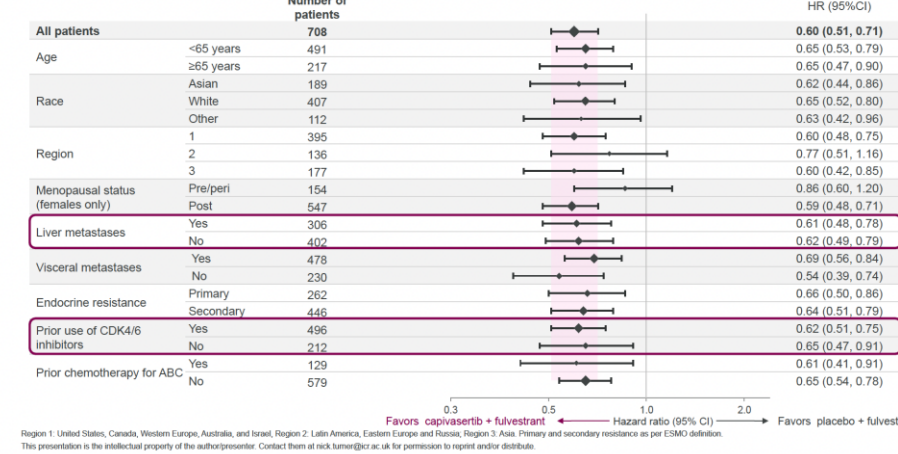
Number of patients at risk

	355	330	266	252	207	199	172	166	138	133	115	98	78	64	55	44	43	25	21	8	8	5	2	2	1	0
Capiasertib + fulvestrant	355	329	267	182	142	136	106	100	83	81	66	59	51	44	33	24	23	13	11	4	4	3	4	1	0	0
Placebo + fulvestrant	353	328	207	182	142	136	106	100	83	81	66	59	51	44	33	24	23	13	11	4	4	3	4	1	0	0

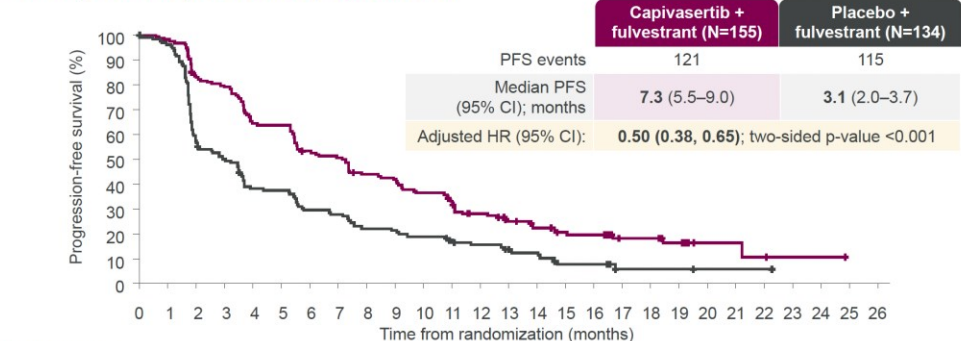
+ indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and prior use of CDK4/6 inhibitor. This presentation is the intellectual property of the author/presenter. Contact them at rick.turner@icr.ac.uk for permission to reprint and/or distribute.

FDA APPROVAL NOV 2023 for AKT pathway-altered pts

Investigator-assessed PFS by subgroup: Overall population



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

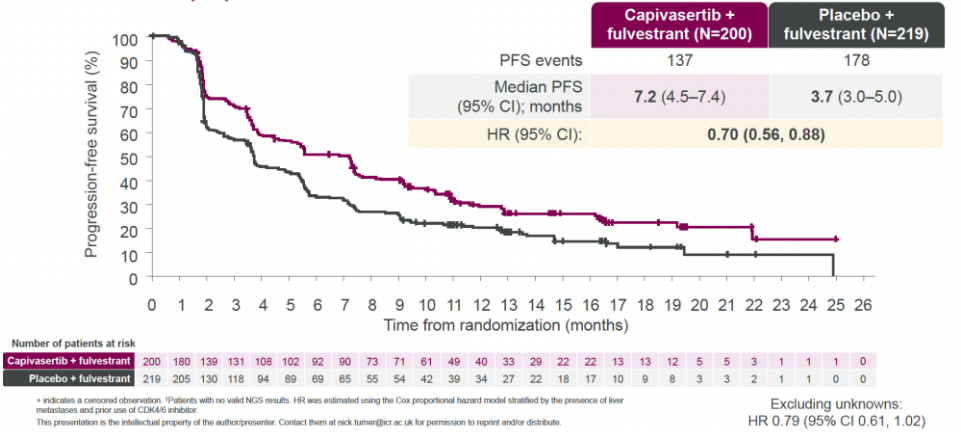


Number of patients at risk

	155	150	137	124	99	87	68	55	46	33	24	17	9	3	3	2	1	1	0	0
Capiasertib + fulvestrant	155	150	137	124	99	87	68	55	46	33	24	17	9	3	3	2	1	1	0	0
Placebo + fulvestrant	134	129	107	99	87	68	55	46	33	24	17	9	3	3	2	1	1	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. This presentation is the intellectual property of the author/presenter. Contact them at rick.turner@icr.ac.uk for permission to reprint and/or distribute.

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



Number of patients at risk

	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	0
Capiasertib + 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	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	0

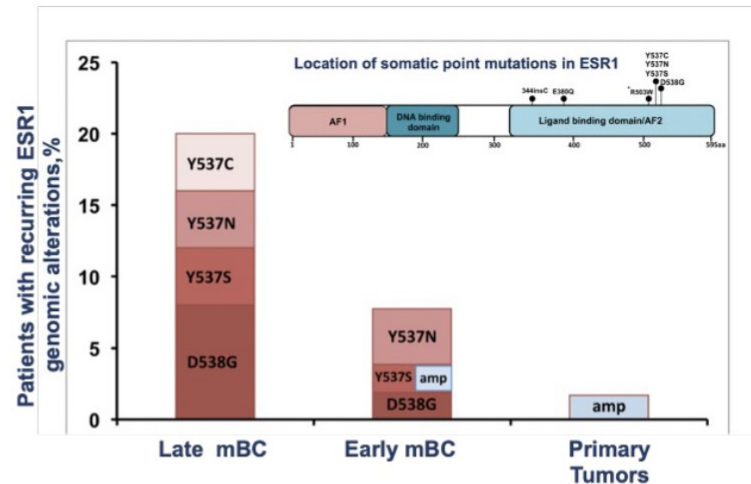
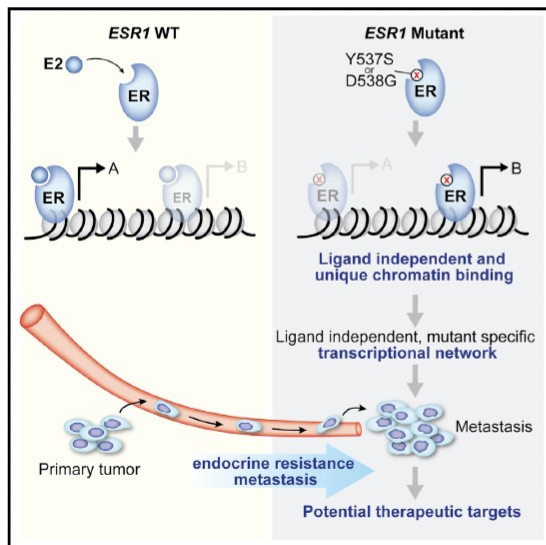
+ indicates a censored observation. [†]Patients with no valid NGS results. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and prior use of CDK4/6 inhibitor. This presentation is the intellectual property of the author/presenter. Contact them at rick.turner@icr.ac.uk for permission to reprint and/or distribute.

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

SERDs / PROTAC / CERAN

ESR1 MUTATIONS

- **ESR1** mutations allow ER α to be activated in the absence of estradiol ⁽¹⁾



- **Major cause of endocrine resistance** ⁽²⁾
 - Primary tumors: not detectable
 - First relapse: rare (< 5%)
 - **Progression on AI: frequent (30-40%)** ⁽³⁾
- **Poor prognostic factor (BOLERO-2)** ⁽⁴⁾
- Predicts **poor response** to AI therapy (SoFEA/EFECT) ⁽⁵⁾
 - Less resistance to fulvestrant, however, limited

(1) Jeselsohn R. *Cancer Cell*. 2018;33(2):173-186.e5

(2) Allouchery V. *Breast Cancer Res*. 2018;20(1):40

(3) Jeselsohn R. *Clin Cancer Res*. 2014;20(7):1757-1767

(4) Chandarlapaty S. *JAMA Oncol*. 2016;2(10):1310-1315

(5) Turner NC. *Clin Cancer Res*. 2020;26(19):5172-5177

EMERGING ER-TARGETING AGENTS

ORAL SERDs

Selective Estrogen
Receptors
Degraders

NOVEL SERMs

Selective Estrogen
Receptors
Modulators

SERCA

Selective Estrogen
Receptor Covalent
Antagonist

PROTAC

Proteolysis
Targeting Chimera

CERAN

Complete Estrogen
Receptor Antagonist

ELACESTRANT

(RAD1901)

GIREDESTRANT

(GDC-9545)

CAMIZESTRANT

(AZD9833)

AMCENESTRANT

(SAR4399859)

IMLUNESTRANT

(LY3484356)

RINTONESTRANT

(G1T48)

BORESTRANT

(ZB-716)

ZN-C5

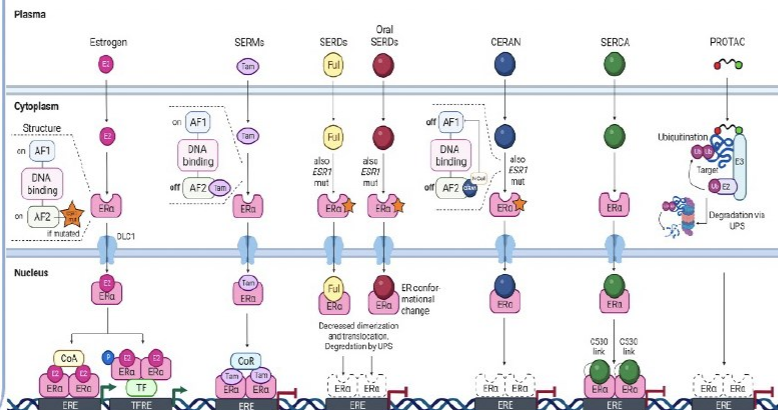
LASOFOXIFENE

BAZEDOXIFENE

H3B-6545

ARV-471

OP-1250



Novel ER-DRIVEN agents differing in potency as **degraders** vs. **antagonistic activity**, which are in **different stages of development** and **different disease contexts**



SINGLE-AGENT SERDs IN PHASE I – II

- Efficacy of select single-agent antiestrogen therapies in phase I and phase I–II non-randomized studies

Class	Drug	Phase Trial	N	Median lines for mBC	Prior CDK 4/6i	Prior Fulvestrant	ESR1 mutation	ORR	CBR	PFS (months)	References
Hybrid SERM/SERD	ELACESTRANT (RAD1901)	I RAD1901-005	50	3 (1-7)	52%	52%	50%	19.4%	42.6%	4.5	Bardia et al. <i>J. Clin. Oncol.</i> 39, 1360–1370 (2021)
SERD	GIREDESTRANT (GDC-9545)	Ia/Ib	111	1 (0-3)	64%	21%	47%	15%	52%	7.2	Jhaveri et al. <i>J. Clin. Oncol.</i> 39, 1017-1017 (2021)
SERD	CAMIZESTRANT (AZD9833)	I SERENA 1	98	3 (0-7)	62%	53%	43%	10%	35.3%	5.4	Baird et al. <i>Cancer Res.</i> 81, PS11-05–PS11-05 (2021)
SERD	IMLUNESTRANT (LY348356)	I EMBER 1	114	2 (0-8)	92%	51%	49%	8%	42%	4.3	Jhaveri et al. <i>J. Clin. Oncol.</i> 40, 1021–1021 (2022)
SERD	RINTODESTRANT (G1T84)	I	67	2 (0-9)	69%	64%	43%	5%	30%	2.6-3.6	Aftimos et al. <i>Cancer Res.</i> 81, PS12-04 (2021)
SERD	ZN-c5	I/II 565TIP	56	2 (0-9)	70%	46%	41%	5%	38%	3.8	Kalinsky et al. <i>Cancer Res.</i> 82, P1-17-02–P11-17-02 (2022)

Oral SERD Trial Landscape in Pretreated mBC

	EMERALD ¹	SERENA-2 ²	EMBER-3 ³	AMEERA-3 ⁴⁻⁶	aceIRA ⁶⁻⁹
Treatment	Elacestrant	Camizestrant	Imlunestrant +/- abemaciclib	Amcenestrant	Giredestrant
Control Arm	fulvestrant / Als	fulvestrant	fulvestrant / exemestane	fulvestrant / Als / tamoxifen	fulvestrant / Als
Phase (n)	Phase 3 (478)	Phase 2 (240)	Phase 3 (800)	Phase 2 (367)	Phase 2 (303)
Patients	Men or postmenopausal women	Postmenopausal women	Men or postmenopausal women	Men or women (any menopausal status)	Men or women (any menopausal status)
Prior CDK4/6i	Required (100%)	Permitted	Permitted	Permitted (79.7%)	Permitted (42%)
Allowed Prior Fulvestrant	YES	NO	NO	YES	YES
Allowed Prior Chemotherapy in mBC	YES	YES	NO	YES	YES
Data readout	Positive (Registrational)	Positive (Non-Registrational)	Ongoing	Negative	Negative

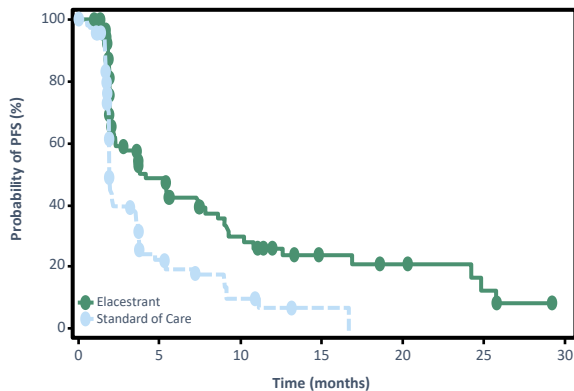
1. Bidard FC, et al. *J Clin Oncol.* 2022;40(28):3246-3256. 2. SERENA2. ClinicalTrials.gov identifier: NCT04214288. Accessed November 18, 2022, <https://clinicaltrials.gov/ct2/show/NCT04214288>; 3. EMBER-3. ClinicalTrials.gov identifier: NCT04975308. Accessed November 18, 2022, <https://clinicaltrials.gov/ct2/show/NCT04975308>; 4. AMEERA3. ClinicalTrials.gov identifier: NCT04059484. Accessed November 18, 2022, <https://clinicaltrials.gov/ct2/show/NCT04059484>; 5. Tolaney SM, et al. *Ann Oncol.* 2022; 33(7):S88-S121 (Abstr 212MO); 6. Evaluate Vantage. <https://www.evaluate.com/vantage/articles/news/trial-results/roche-has-rare-breast-cancer-setback>. Accessed July 20, 2022; 7. aceIRA ClinicalTrials.gov identifier: NCT04576455. Accessed November 18, 2022, <https://clinicaltrials.gov/ct2/show/NCT04576455>; 8. Martin M, et al. *J Clin Oncol.* 2021;39(15):abstr TPS1100; 9. Martin Jimenez M, et al. *Ann Oncol.* 2022;33(7):S88-S121 (abstr 211MO).

Modified from Kaklamani V et al., *GS3-01 EMERALD phase 3 trial of elacestrant versus standard of care endocrine therapy in patients with ER+/HER2- metastatic breast cancer: Updated results by duration of prior CDK4/6i in metastatic setting*. Abstract GS3-01; SABCS 2022

EMERALD:

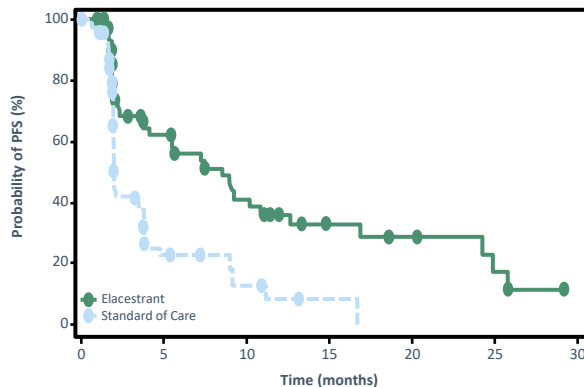
Patients with *ESR1*-mut Tumors: PFS by Duration of CDK4/6i

At least 6 mo CDK4/6i



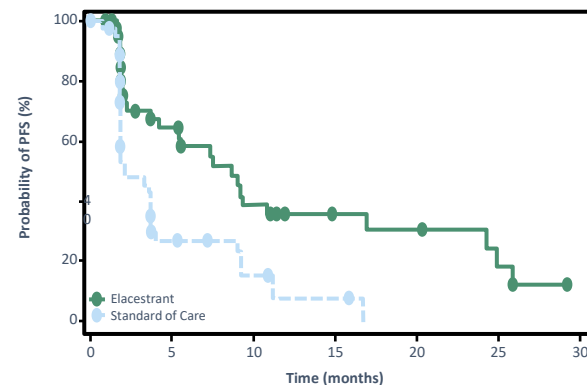
Elacestrant 103 50 33 25 20 16 11 9 8 7 6 5 5 1 1 0
SOC 102 34 16 11 9 5 2 1 1 0

At least 12 mo CDK4/6i



Elacestrant 78 42 31 24 20 16 11 9 8 7 6 5 5 1 1 0
SOC 81 26 12 10 9 5 2 1 1 0

At least 18 mo CDK4/6i



Elacestrant 55 30 23 18 16 12 8 8 7 6 6 5 5 1 1 0
SOC 56 21 9 8 7 4 1 1 1 0

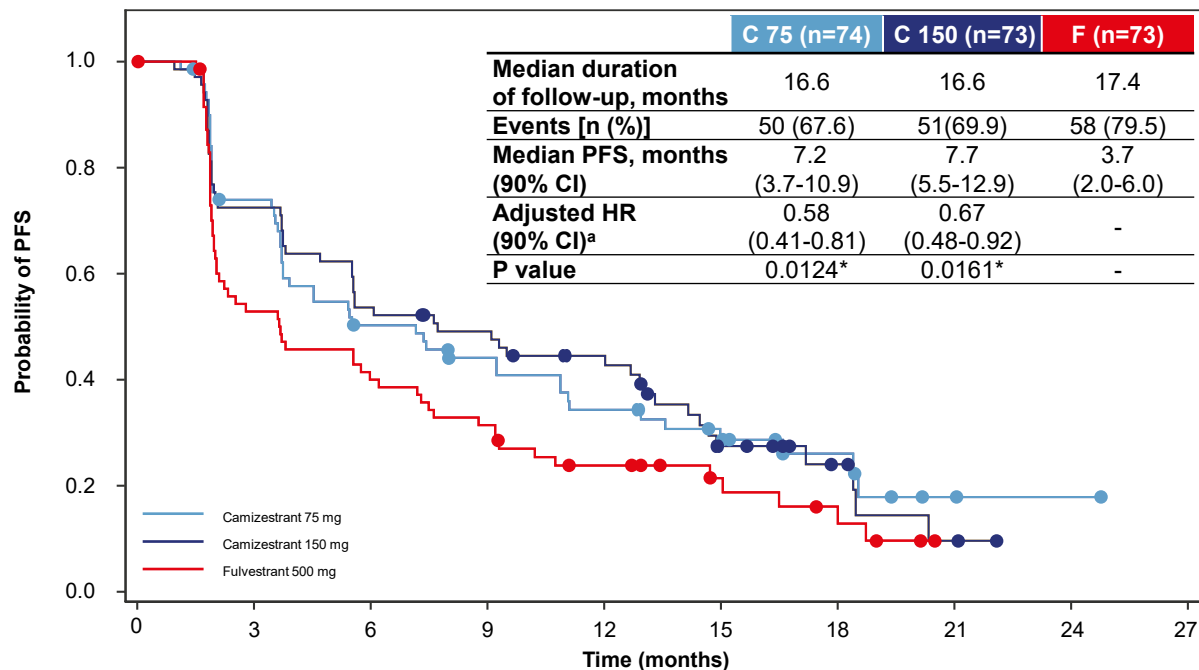
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	4.14 (2.20 - 7.79)	1.87 (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	0.517 (0.361 - 0.738)	

	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)	

	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)	

Modified from Kaklamani V et al., GS3-01 EMERALD phase 3 trial of elacestrant versus standard of care endocrine therapy in patients with ER+/HER2- metastatic breast cancer: Updated results by duration of prior CDK4/6i in metastatic setting. Abstract GS3-01; SABCS 2022

SERENA 2: Primary endpoint: PFS by investigator assessment



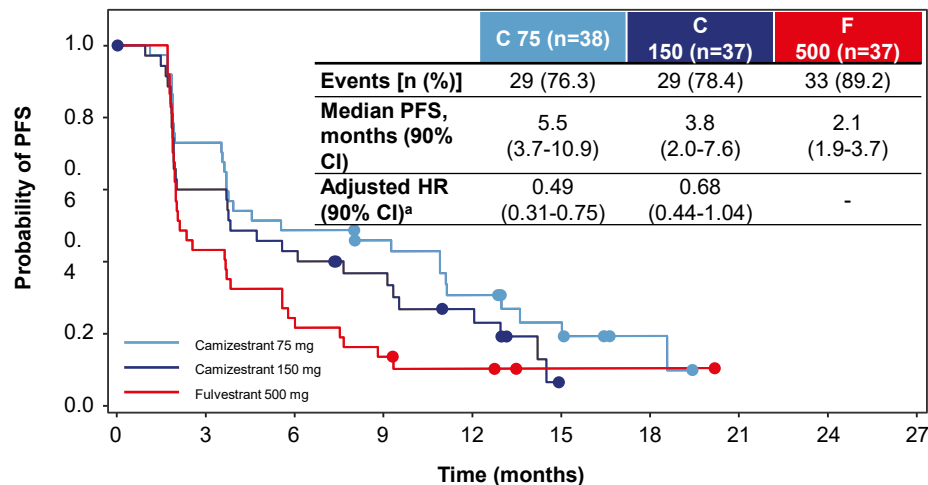
In the overall population, camizestrant produces a statistically significant and clinically meaningful improvement in PFS for both 75 and 150 mg camizestrant doses over fulvestrant

*Statistically significant; ^aHRs 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

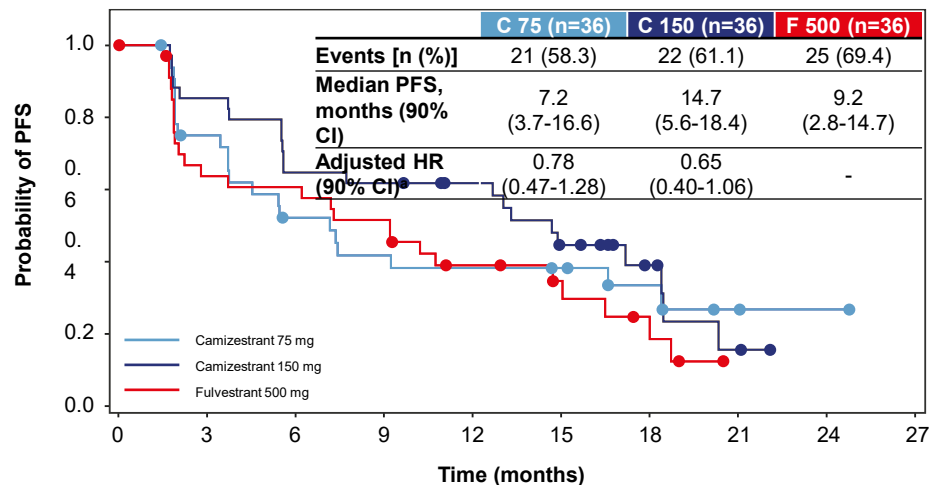
SERENA 2: Primary endpoint: PFS by prior CDKi

Prior CDK4/6i



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	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

^aHRs adjusted for liver/lung metastases

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

IN COMBINATION WITH CDK4/6i

- Efficacy oral SERDs with CDK4/6i in phase I trials

Drugs	N	Prior CDK4/6i (%)	ORR (%)	CBR(%)	References
CAMIZESTRANT PALBOCICLIB	48	69	6.3	50	<i>Baird et al. SABCS 2020 (PS 11-05)</i>
AMCENESTRANT PALBOCICLIB	35	5.1	34.3	74.3	<i>Chandarlapaty S et al. ASCO 2021 (abs 1058)</i>
GIREDISTRANT PALBOCICLIB	48	0	33	81	<i>Lim E et al. ASCO 2020 (abs 1023)</i>
IMLUNESTRANT ABEMACICLIB	42	0	32	71	<i>Jhaveri K et al. SABCS 2022 (abs PD 13-12)</i>
RINTODESTRANT PALBOCICLIB	40	0	5	61	<i>Maglakelidze M et al. ASCO 2021 (abs 1023)</i>

SERENA – 4
N=1342
No prior tx for ABC
PFS
NCT04711252

1:1

Camizestrant 75 mg
Palbociclib 125 mg
Anastrozole – matched PLA

Anastrozole 1 mg
Palbociclib 125 mg
Camizestrant – matched PLA

persevERA
N=978
No prior tx for ABC
PFS
NCT04546009

1:1

Giredestrant 30 mg
Palbociclib 125 mg
Letrozole – matched PLA

Letrozole 1 mg
Palbociclib 125 mg
Giredestrant – matched PLA

EMBER-3
N=869
No prior fulvestrant
Allowed tx CDK4/6i
PFS
NCT04188548

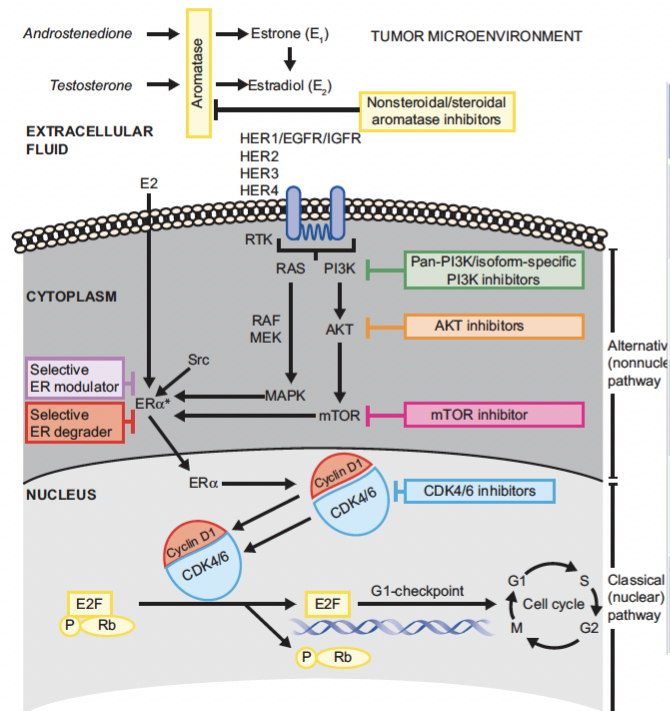
1:1:1

Imlunestrant 400 mg

Investigator's choice ET
(Fulvestrant or exemestane)

Imlunestrant 400 mg
Abemaciclib 150 mg BD

IN COMBINATION WITH TARGETED AGENTS



Adapted from Brufsky AM Oncologist. 2018;23(5):528-539

Drug	Trial ID	Combination drugs	Primary endpoint	Patient population
ELACESTRANT (RAD1901)	ELEVATE Phase Ib/II (NCT05563220)	Alpelisib, Everolimus, Abemaciclib	DLT RP2D	mBC, ≥ 1L ET
GIREDESTRANT (GDC-9545)	MORPHEUS Phase Ib/II (NCT04802759)	Abemaciclib, Palbociclib, ribociclib, ipatasertib, inavolisib, everolimus, samuraciclib	ORR	mBC, 2 nd /3 rd line
GIREDESTRANT (GDC-9545)	evERA Phase III (NCT053063340)	Combined with everolimus vs everolimus + exemestane	PFS	mBC, 2 nd /3 rd line
CAMIZESTRANT (AZD9833)	SERENA-1 Phase I (NCT4214288)	Abemaciclib, everolimus, capivasertib	DLT	mBC, ≥ 2L ET
IMLUNESTRANT (LY348356)	EMBER-1 Phase I (NCT 4188548)	Alpelisib, abemaciclib, everolimus, trastuzumab, trastuzumab-abemaciclib	DLT	mBC, HER2-positive or negative

HR+/HER2– ABC after 1st-line CDKi progression (randomised data)

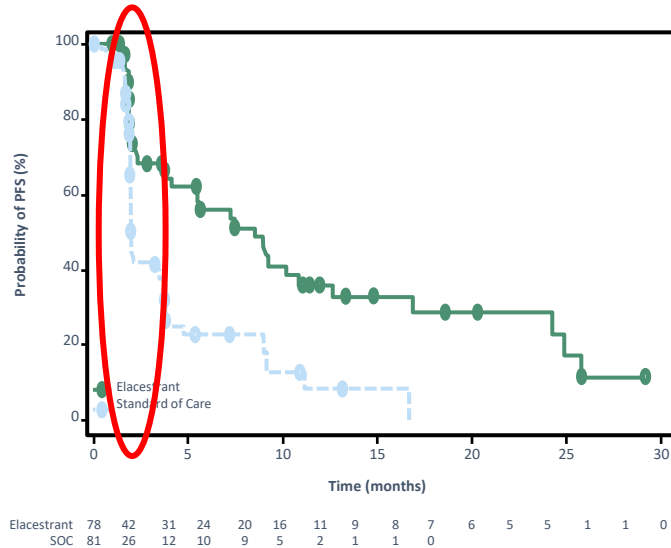
Drug	Trial	Prior CDKi	mPFS
Giredestrant	aceLERA ¹	41%	5.6 months (independent of <i>ESR1</i> mutation)
Amcenestrant	AMEERA-3 ²	80%	3.6 months (independent of <i>ESR1</i> mutation)
Elacestrant	EMERALD ³	100%	8.6 months (<i>ESR1</i> mutation and >12 months ILP 1st-line treatment)
Camizestrant	SERENA-2 ⁴	50%	9.2 months (150 mg and <i>ESR1</i> mutation)
Lasofloxifene	Goetz, ESMO22 ⁵	100%	6.04 months
ARV-471	VERITAC-2 ⁶	100%	5.5 months (<i>ESR1</i> mutation)
Venetoclax	VERONICA ⁷	100%	2.69 months
Fulvestrant	VERONICA ⁷	100%	1.94 months
Ribociclib	MAINTAIN ⁸	100%	5.3 months
Palbociclib	PACE ⁹	100%	4.6 months
Palbociclib	PALMIRA ¹⁰	100%	4.9 months
Capivasertib	CAPItello-291 ¹¹	70%	7.2 months
Alpelisib	BYLieve ^{12*}	100%	7.3 months (cohort A)

These data are from the relevant clinical studies and not intended to represent comparison between treatments.

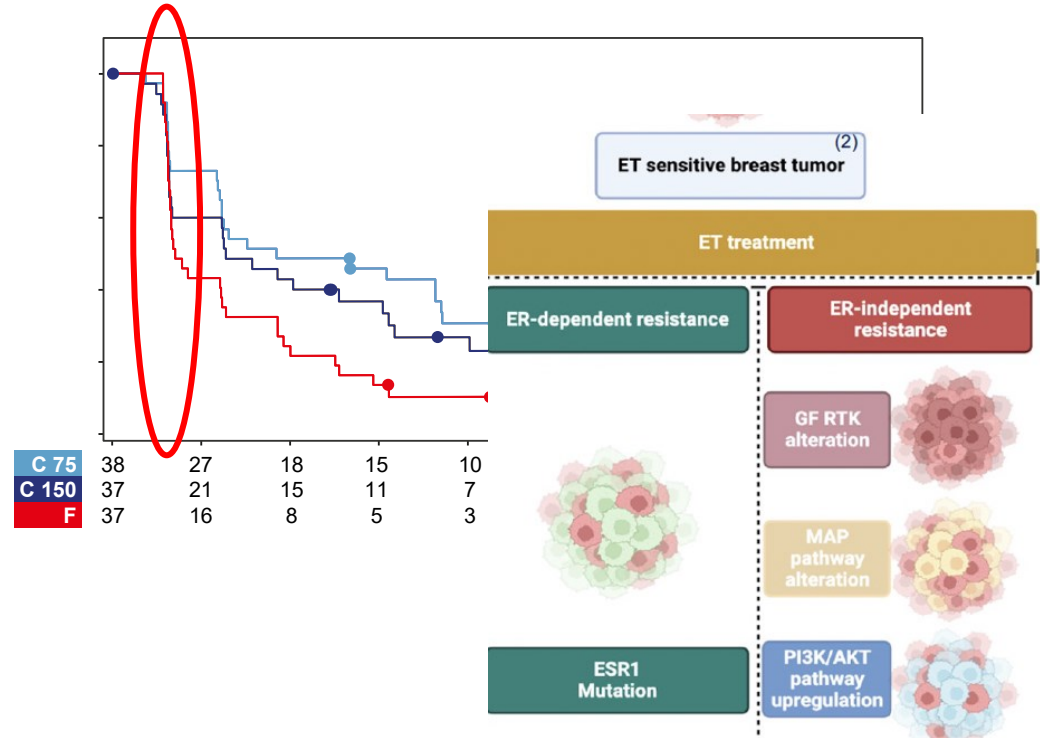
Early biomarkers of progression to CDKi

30% pts are early progressors to 2nd line ET (monotherapy)

EMERALD



SERENA 2



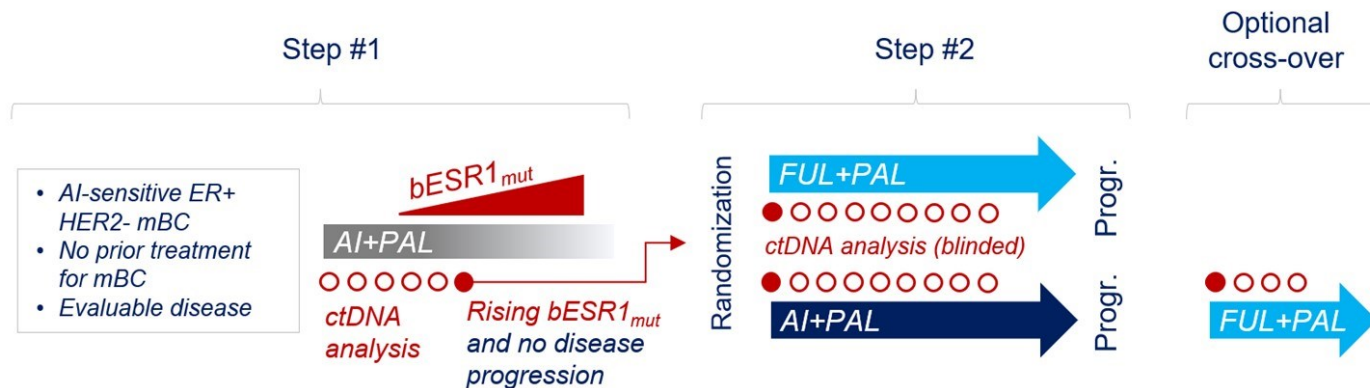
Background: $ESR1_{mut}$ & PADA-1 design

$ESR1$ mutations

- are acquired during aromatase inhibitors (AI) therapy in ~40% of ER+ HER2- mBC pts and drive resistance
- can be detected by ctDNA analysis in blood ($bESR1_{mut}$)
- retain partial sensitivity to fulvestrant (FUL), a selective estrogen receptor degrader (SERD)

PADA-1

- Strategy: **targeting rising $bESR1_{mut}$ when they become detectable** under AI+Palbociclib (PAL) ^[1]



^[1] Berger *et al.*, BMJ Open 2022

PADA-1 Trial

Bidard, et al

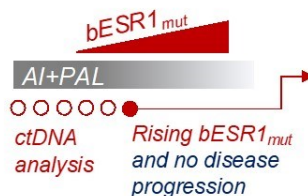
Dynamics and type of *ESR1* mutations under AI or fulvestrant combined with palbociclib after randomization in the PADA-1 trial

L. Cabrel, S. Delalogue, AC Hardy-Bessard, F. André, T. Bachelot, J. Blanche, C. Calais, A. Pradines, F. Clotet, T. de la Motte Rouge, J. Canon, L. Arnould, B. Pignatelli, F. Dalenc, R. Sabatier, J. Ferrero, A. Lortholary, J. Lecomte, F. Berger, EC Bidard

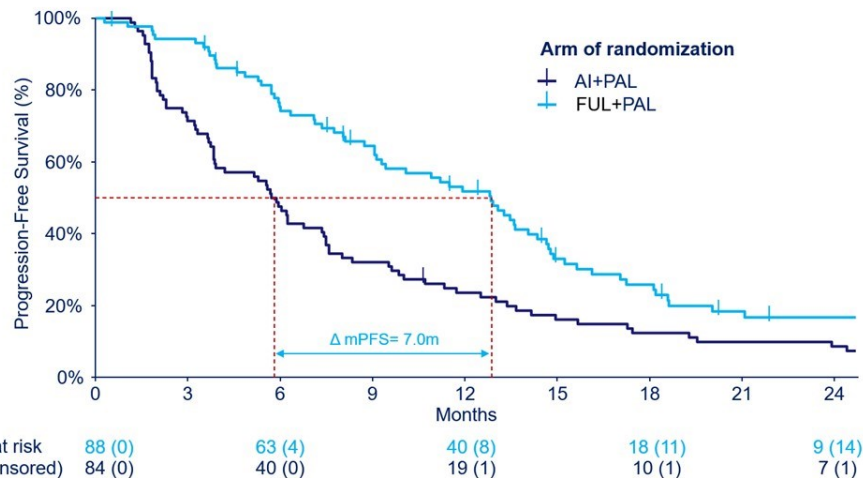
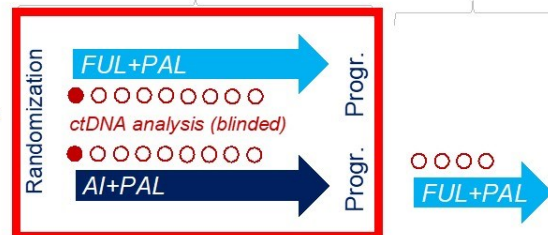


- AI-sensitive ER+ HER2- mBC
- No prior treatment for mBC
- Evaluable disease

Step #1



Step #2



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]

PADA-1 Trial

Bidard, et al

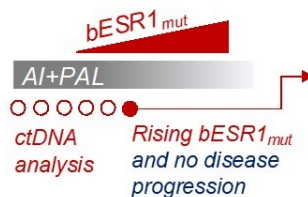
Dynamics and type of *ESR1* mutations under AI or fulvestrant combined with palbociclib after randomization in the PADA-1 trial

L. Cabrel, S. Delalogue, AC Hardy-Bessard, F. André, T. Bachelot, J. Blanche, C. Calais, A. Pradines, F. Clotet, T. de la Motte Rouge, J. Canon, L. Arnould, B. Pignatelli, F. Dalenc, R. Sabatier, J. Ferrero, A. Lortholary, J. Lecomte, F. Berger, EC Bidard

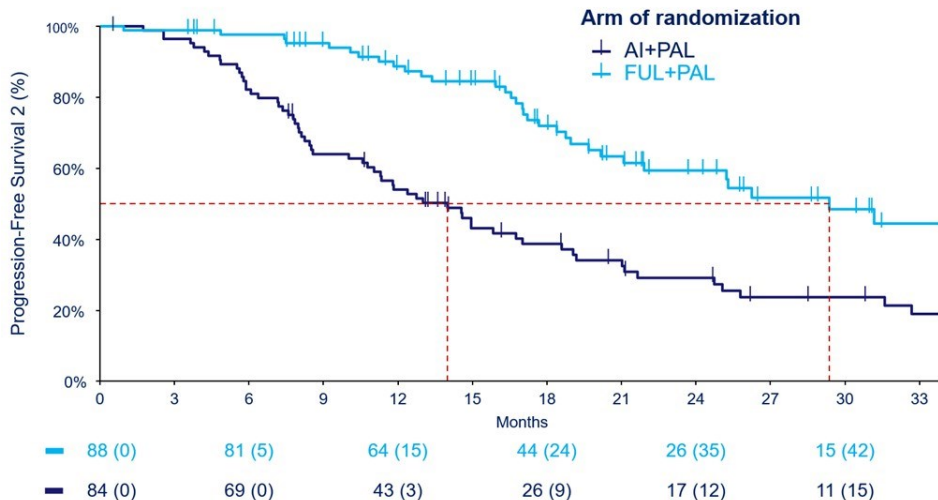
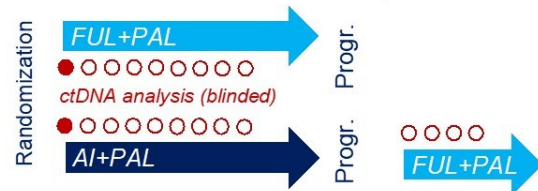


- AI-sensitive ER+ HER2- mBC
- No prior treatment for mBC
- Evaluable disease

Step #1



Step #2



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



SERENA-6

- Ongoing randomised, double-blind study to evaluate the safety and efficacy of camizestrant (AZD9833) in combination with CDK4/6i (palbociclib or abemaciclib) vs AI (anastrozole or letrozole) + CDK4/6i in patients with HR+/HER2- mBC with detectable *ESR1*m^{1,2}



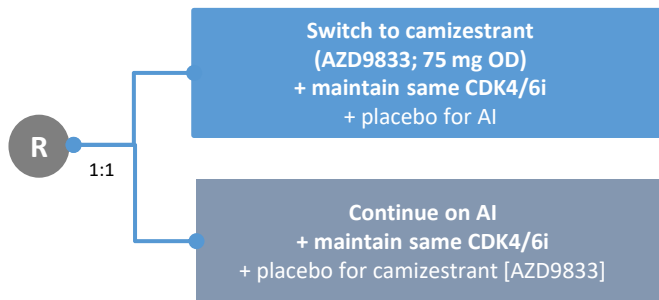
- Adults with HR+/HER2- mBC currently receiving AI (anastrozole or letrozole) + CDK4/6i (palbociclib or abemaciclib) ± LHRH as 1L treatment for advanced disease for ≥6m^{1,2}
- ESR1*m positive tumour detected by plasma ctDNA with no evidence of disease progression by investigator assessment^{1,2}

Estimated enrollment: 302 participants¹

Start date: June 2021¹

Recruitment status: Recruiting¹

Estimated study completion date: June 2026¹



Primary endpoint^{1,2}

- PFS^a

Secondary endpoints^{1,2}

- PFS2
- OS
- Chemotherapy-free survival
- ORR
- CBR₂₄
- PROs

Safety and tolerability²

- AEs, SAEs, vital signs, clinical safety laboratory assessments



ClinicalTrials.gov Identifier:
NCT04964934

Eligibility Criteria



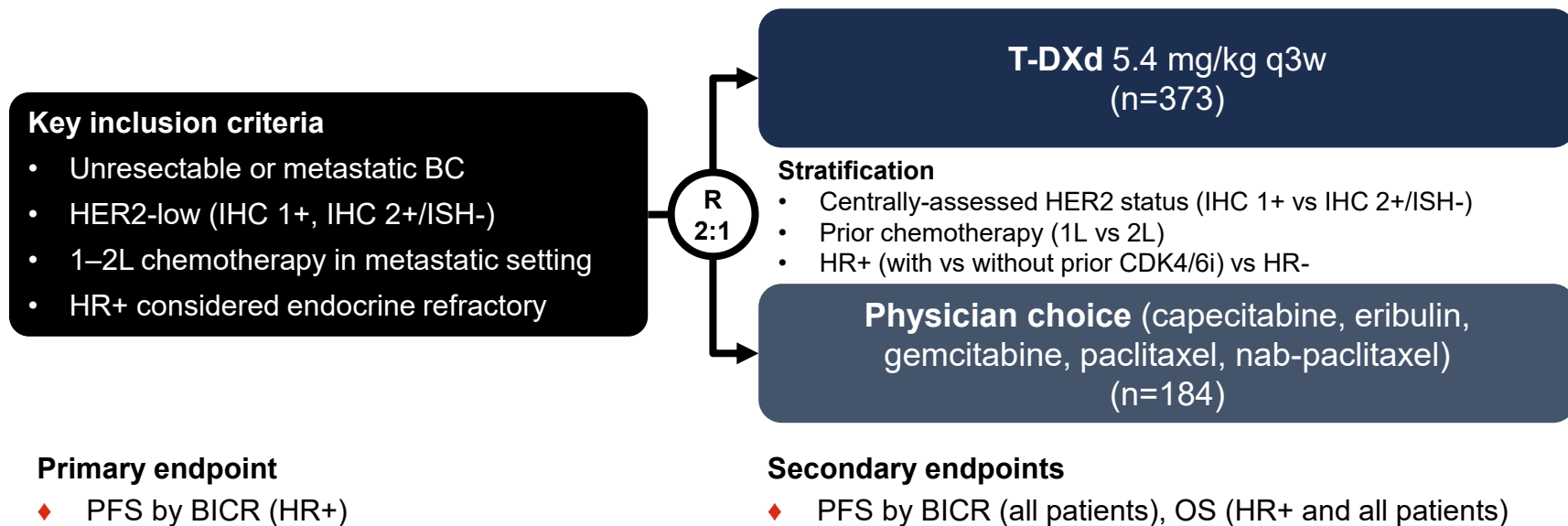
^aAssessed by investigator assessment per RECIST version 1.1. 1L: first-line; AE: adverse event; AI: aromatase inhibitor; CBR₂₄: clinical benefit rate at 24 weeks; ctDNA: circulating tumour DNA; CDK4/6i: cyclin-dependent kinase 4/6 inhibitor; *ESR1*m: estrogen receptor 1 mutation; *HER2*: human epidermal growth factor receptor 2; HR: hormone receptor; LHRH: luteinising hormone-releasing hormone; mBC: metastatic breast cancer; OD: once daily; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PFS2: second progression-free survival; SAE: serious adverse event; QoL: quality of life R: randomisation. 1. Study [NCT04964934](https://clinicaltrials.gov/ct2/show/study/NCT04964934). ClinicalTrials.gov website. 2. Bidard F-C et al. Poster presented at: SABCS; December 7–10, 2021; Virtual. Poster OT2-11-05.

ADCs

DESTINY-Breast04 Study design

Objective

- To evaluate the efficacy and safety of trastuzumab deruxtecan (T-DXd) in patients with HER2-low unresectable or metastatic BC in the DESTINY-Breast04 trial



DESTINY-Breast04 PFS

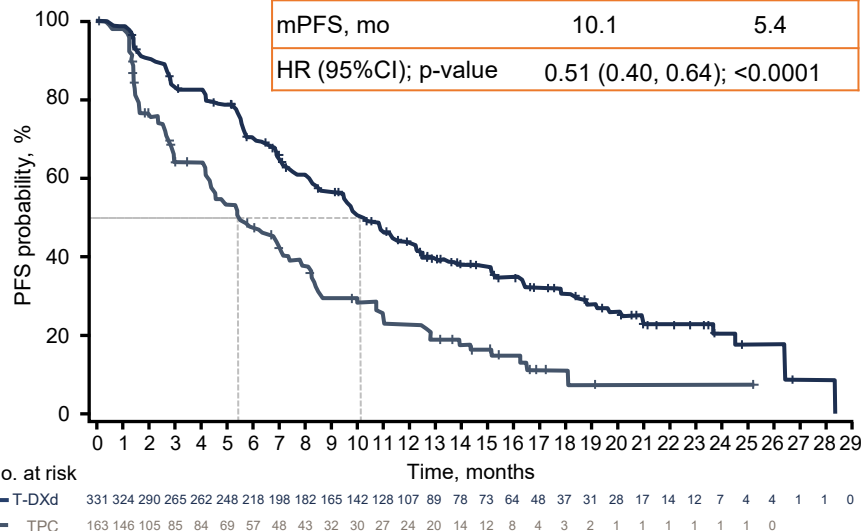
PFS

HR+

T-DXd

Physician
choice

mPFS, mo	10.1	5.4
HR (95%CI); p-value	0.51 (0.40, 0.64); <0.0001	

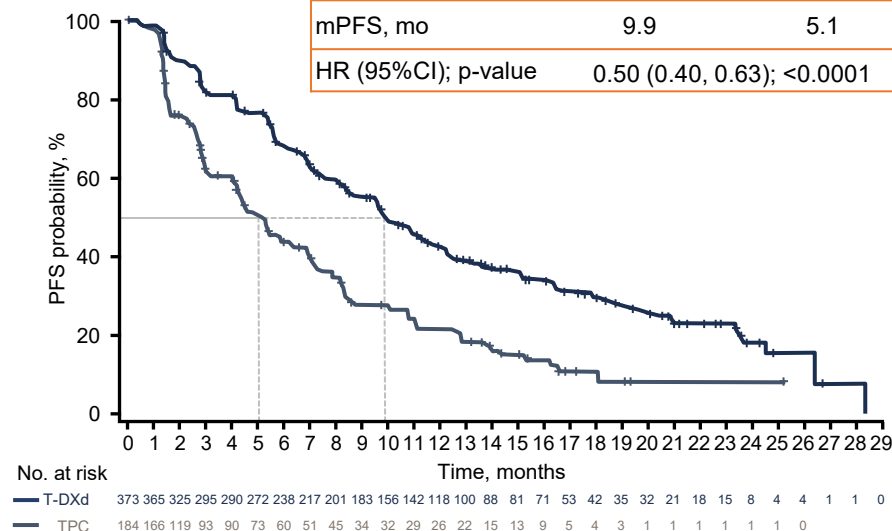


All patients

T-DXd

Physician
choice

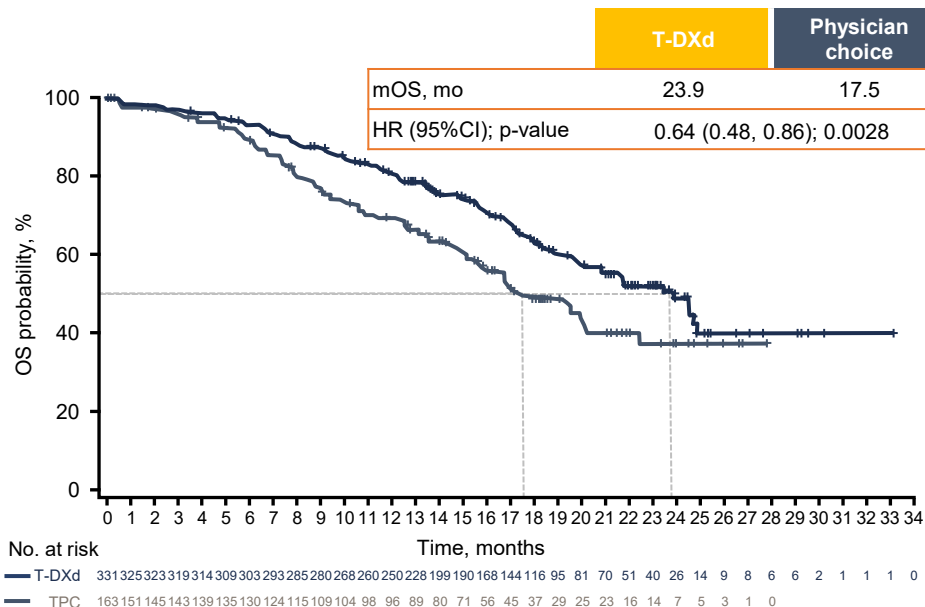
mPFS, mo	9.9	5.1
HR (95%CI); p-value	0.50 (0.40, 0.63); <0.0001	



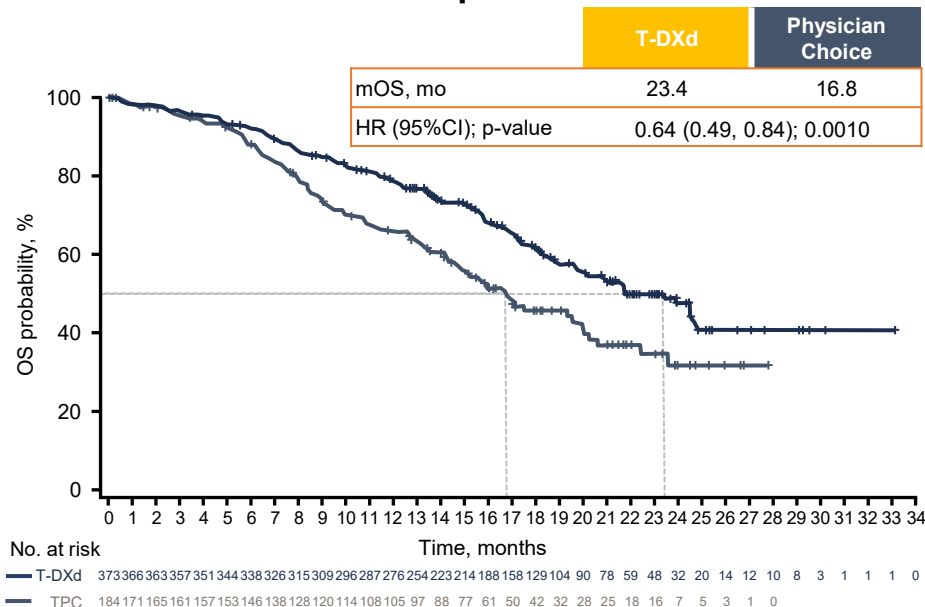
DESTINY-Breast04 OS

OS

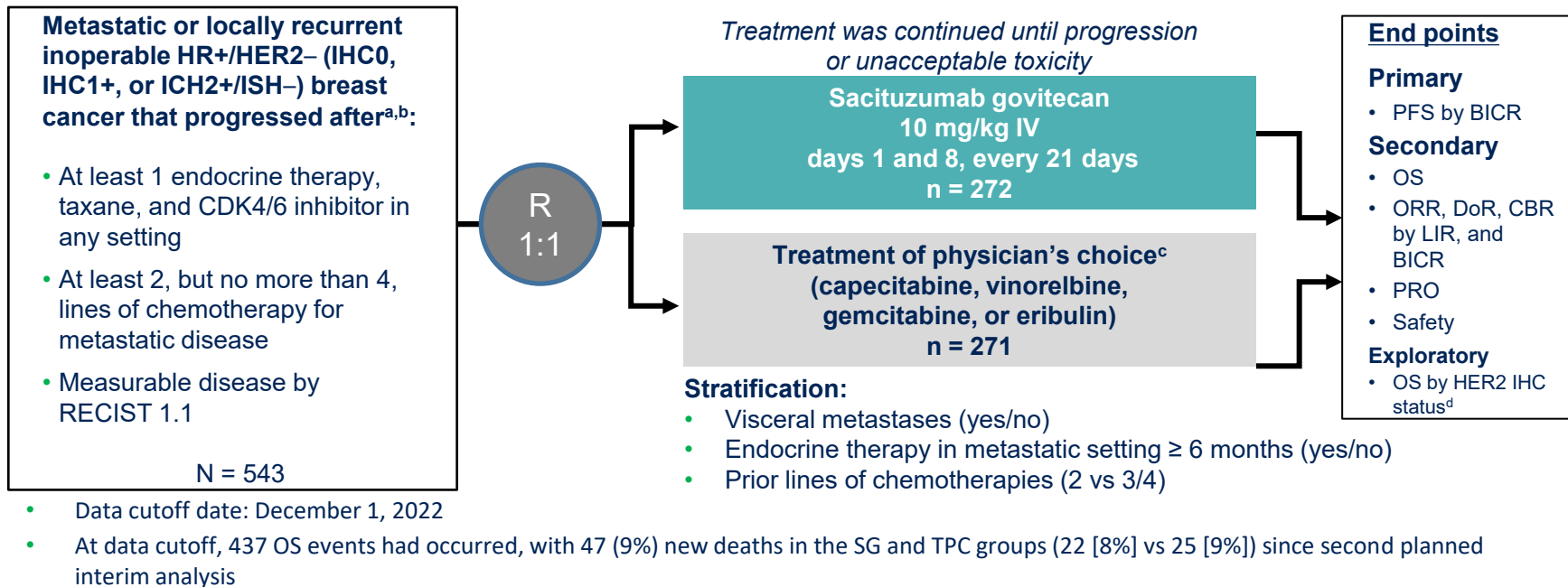
HR+



All patients



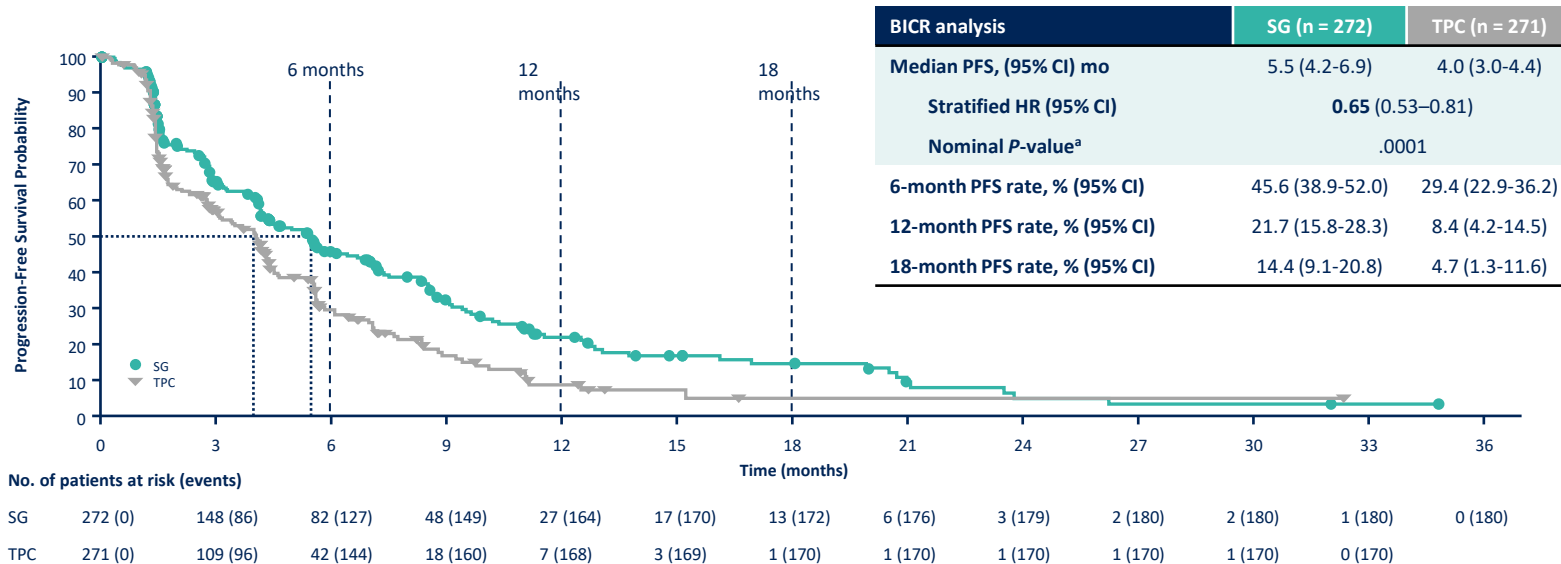
TROPiCS-02: A Phase 3 Study of SG in Patients with HR+/HER2- mBC¹



ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; DoR, duration of response; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormonal receptor-positive; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenously; LIR, local investigator review; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcomes; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors. 1. Ruco HS, et al. *J Clin Oncol.* 2022;40:3365-3376.

^aClinicalTrials.gov. NCT03901339. ^bDisease histology based on the ASCO/CAP criteria. ^cSingle-agent standard-of-care treatment of physician's choice was specified prior to randomization by the investigator. ^dHER2-low was defined as IHC score of 1+, or score of 2+ with negative ISH result; HER2 IHC0 was defined as IHC score of 0.

Progression-Free Survival

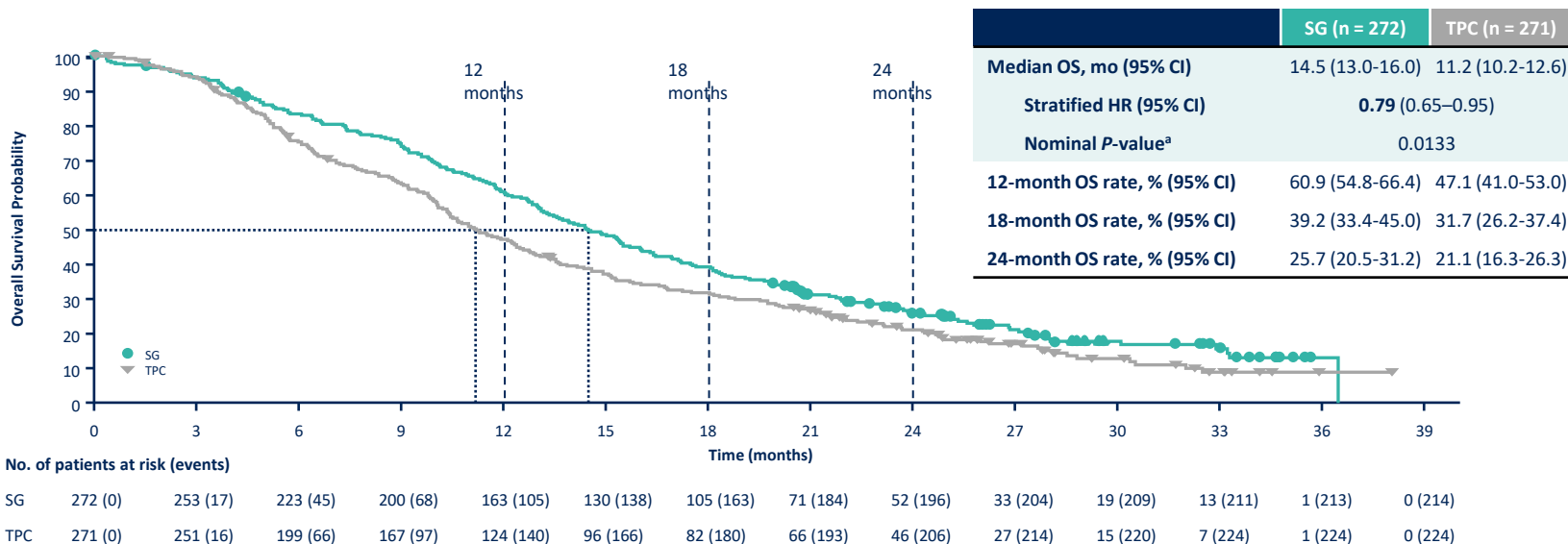


SG continued to demonstrate improvement in PFS vs TPC at longer follow-up, with 35% reduction in risk of disease progression or death, and a higher proportion of patients remained alive and progression-free at each landmark

^aStratified log rank P-value.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

TROPICS02: Overall Survival



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

^aStratified log rank P-value.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

TROPION-Breast01 Study Design¹

Randomised, phase 3, open-label, global study (NCT05104866)

Key inclusion criteria:

- Patients with HR+/HER2– breast cancer* (HER2– defined as IHC 0/1+/2+; ISH negative)
- Previously treated with 1–2 lines of chemotherapy (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

1:1

Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=365)

Investigator's choice of chemotherapy (ICC)
as per protocol directions†
(eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1,8 Q3W; capecitabine D1–14 Q3W)
(n=367)

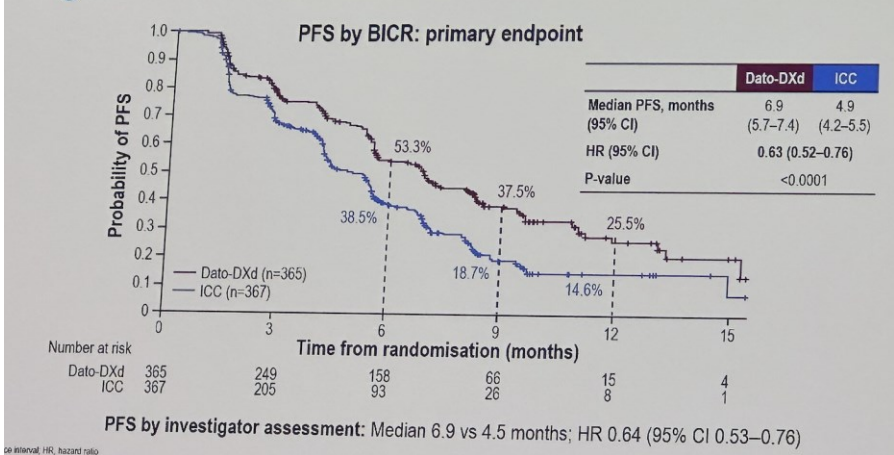
Randomisation stratified by:
• **Lines of chemotherapy** in unresectable/metastatic setting (1 vs 2)
• **Geographic location** (US/Canada/Europe vs ROW)
• **Previous CDK4/6 inhibitor** (yes vs no)

- Treatment continued until PD, unacceptable tolerability, or

Demographics and Baseline Characteristics

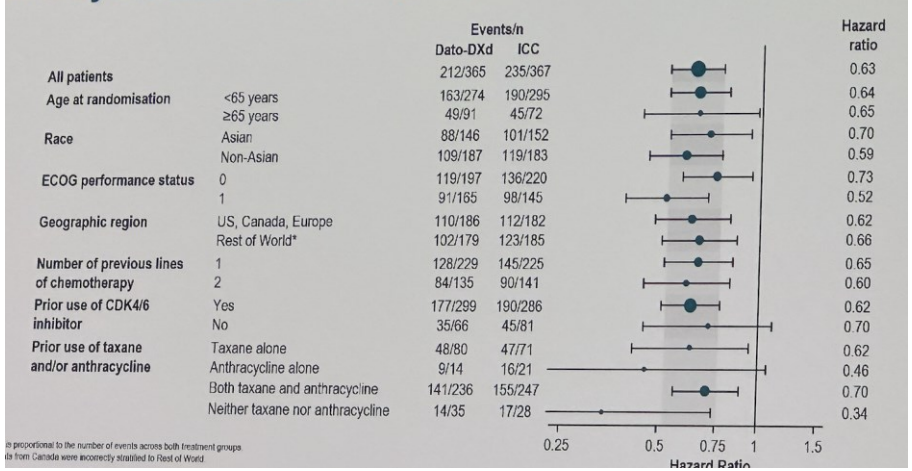
		Dato-DXd (n=365)	ICC (n=367)
Age, median (range), years		56 (29–86)	54 (28–86)
Female, n (%)		360 (99)	363 (99)
Race, n (%) Black or African American / Asian / White / Other*		4 (1) / 146 (40) / 180 (49) / 35 (10)	7 (2) / 152 (41) / 170 (46) / 38 (10)
Ethnicity, n (%) Hispanic or Latino / Not Hispanic or Latino†		40 (11) / 322 (88)	43 (12) / 318 (87)
Prior lines of chemotherapy,‡ n (%) 1 / 2		229 (63) / 135 (37)	225 (61) / 141 (38)
Prior CDK4/6 inhibitor, n (%) Yes / No		299 (82) / 66 (18)	286 (78) / 81 (22)
Prior taxane and/or anthracycline, n (%)	Taxane and/or Anthracycline	330 (90)	339 (92)
	Neither	35 (10)	28 (8)

Progression-Free Survival



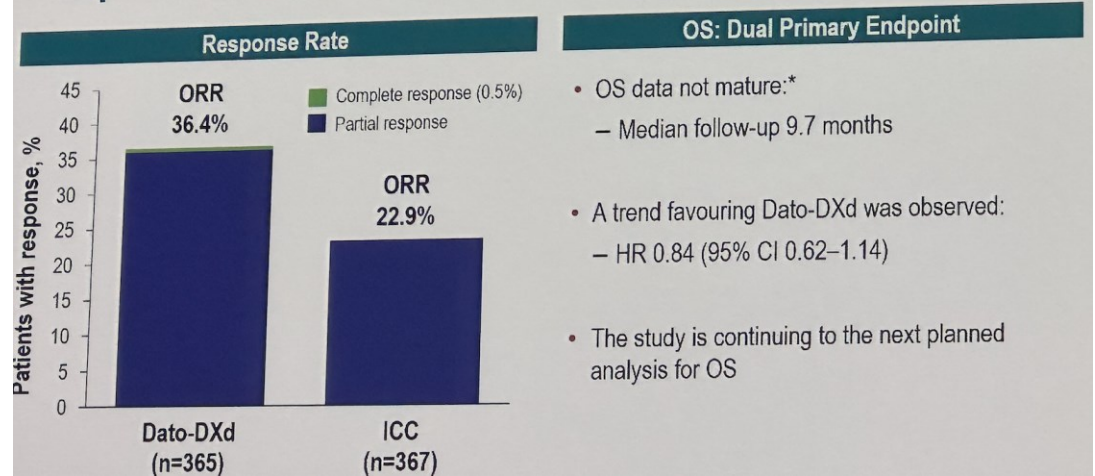
on interval: HR, hazard ratio

PFS by BICR Across Subgroups

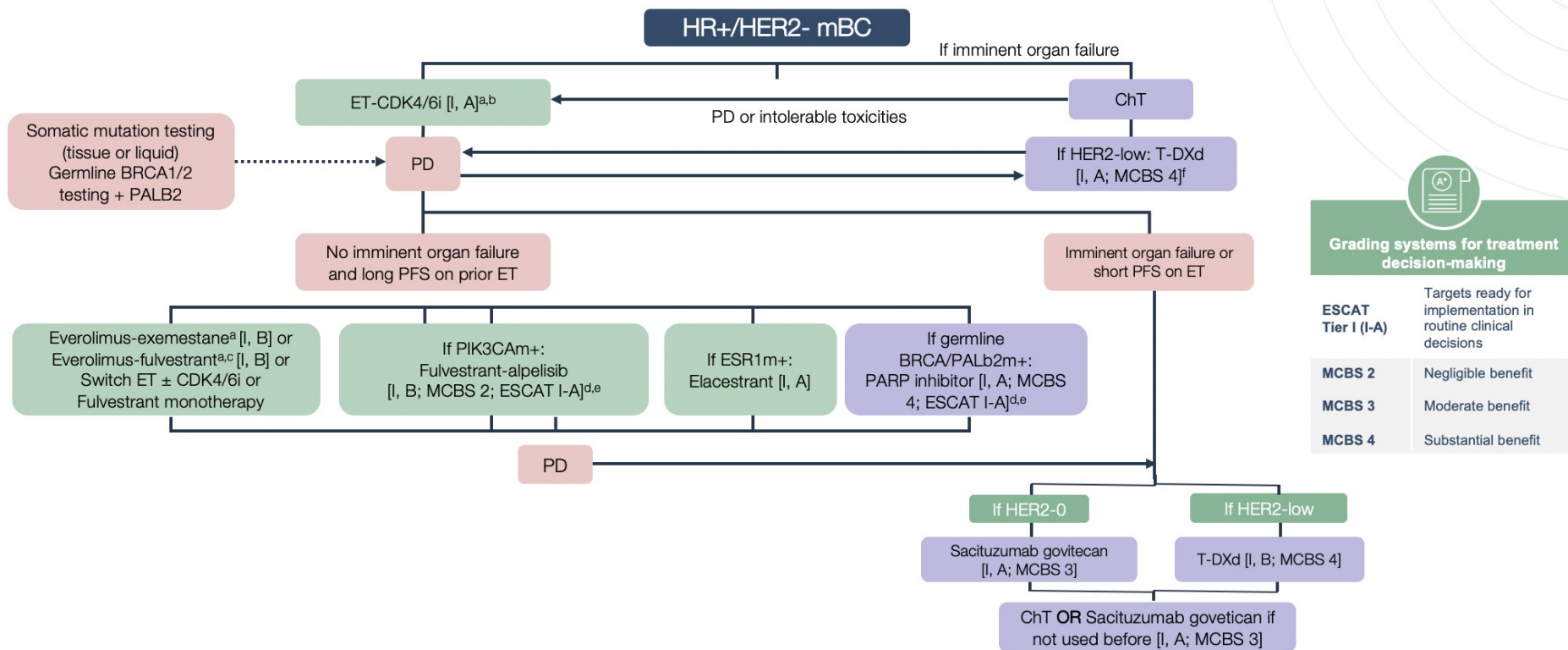


* is proportional to the number of events across both treatment groups
* is from Canada were incorrectly stratified to Rest of World

Response and Interim OS



ESMO guidelines for HR+/HER2- mBC



^aOvarian function suppression if patient is premenopausal, ^bIf relapse <12 months after end of adjuvant AI: fulvestrant-CDK4/6 inhibitor (a); if relapse >12 months after end of adjuvant AI: AI-CDK4/6 inhibitor (a), ^cPreferred if the patient is ESR1 mutation positive [ESCAT score: II-A]. (d), ^eESMO-MCBS v1.1 (Cherny, 2017) was used to calculate scores for new therapies/indications approved by the EMA or FDA, ^fESCAT scores apply to genomic alterations only, T-DXd can also be given following adjuvant ChT in the setting of fast progression.

HR pos HER2 neg MBC sequencing 2025

Factors influencing treatment decision upon progression:

- Prior ET
- Symptoms
- Somatic mts ESR1, PIK3CA, AKT, PTEN
- BRCA1/2
- Response to prior ET + CDK4/6i (> or < 12 mo)

AI + CDK4/6i

