Improving Outcomes with First-Line Endocrine-Based Therapy for Patients with HR-Positive, HER2-Negative Metastatic Breast Cancer

A CME/MOC-Accredited Live Webinar

Tuesday, October 8, 2024
5:00 PM – 6:00 PM ET

Faculty

Francois-Clement Bidard, MD, PhD
Kevin Kalinsky, MD, MS

Moderator

Neil Love, MD

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Faculty

Francois-Clement Bidard, MD, PhD
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MODERATOR
Neil Love, MD
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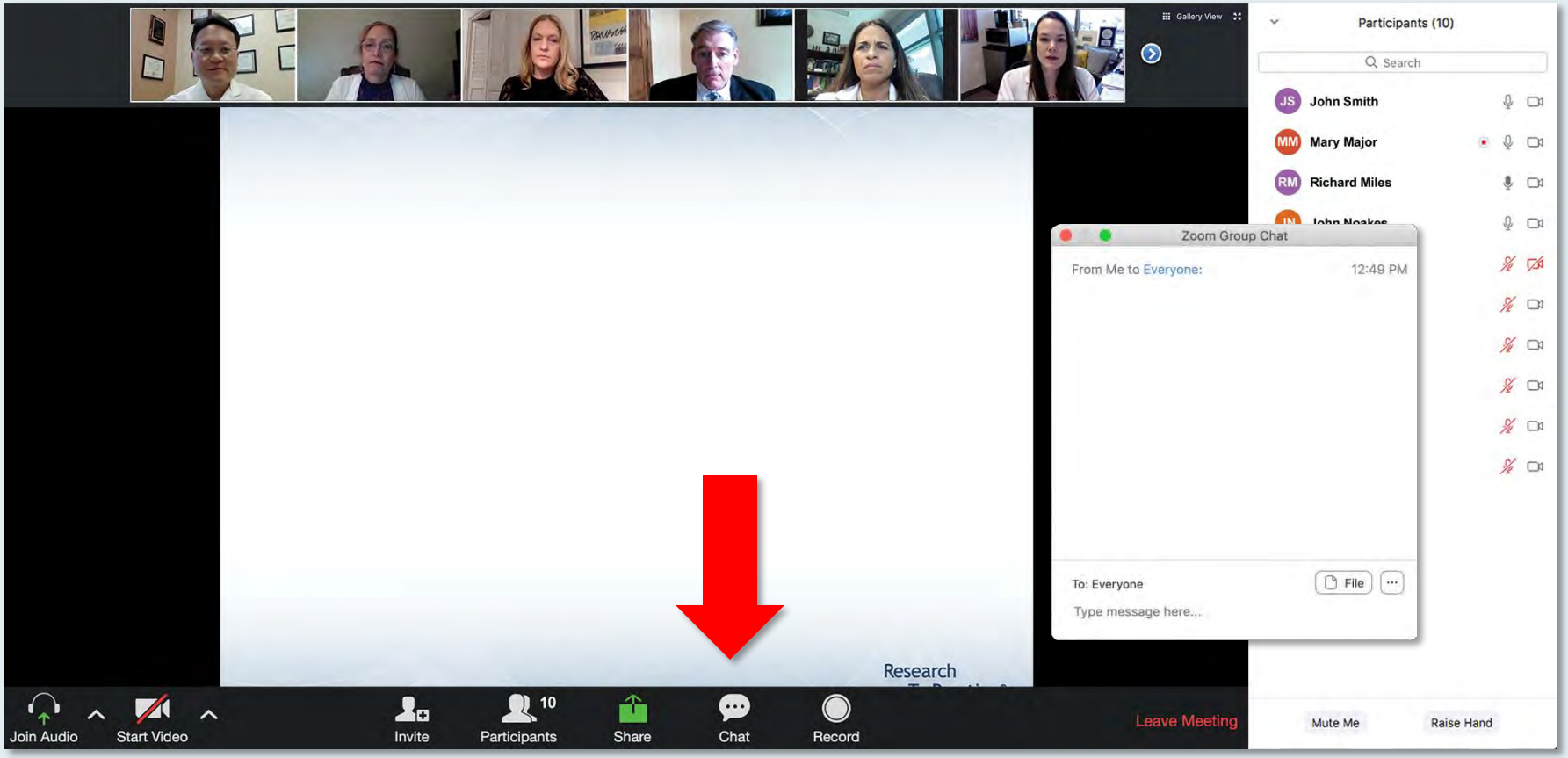

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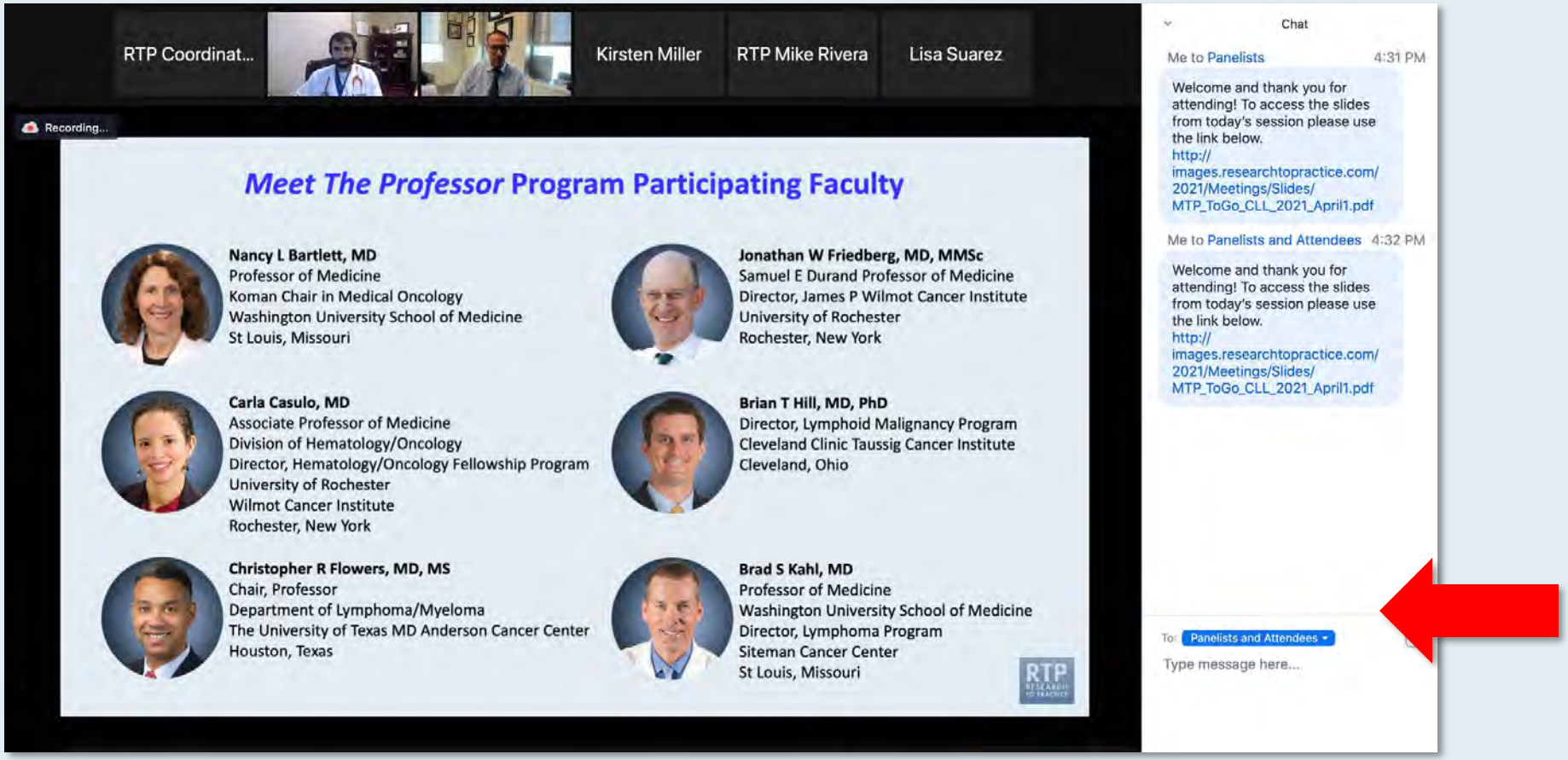

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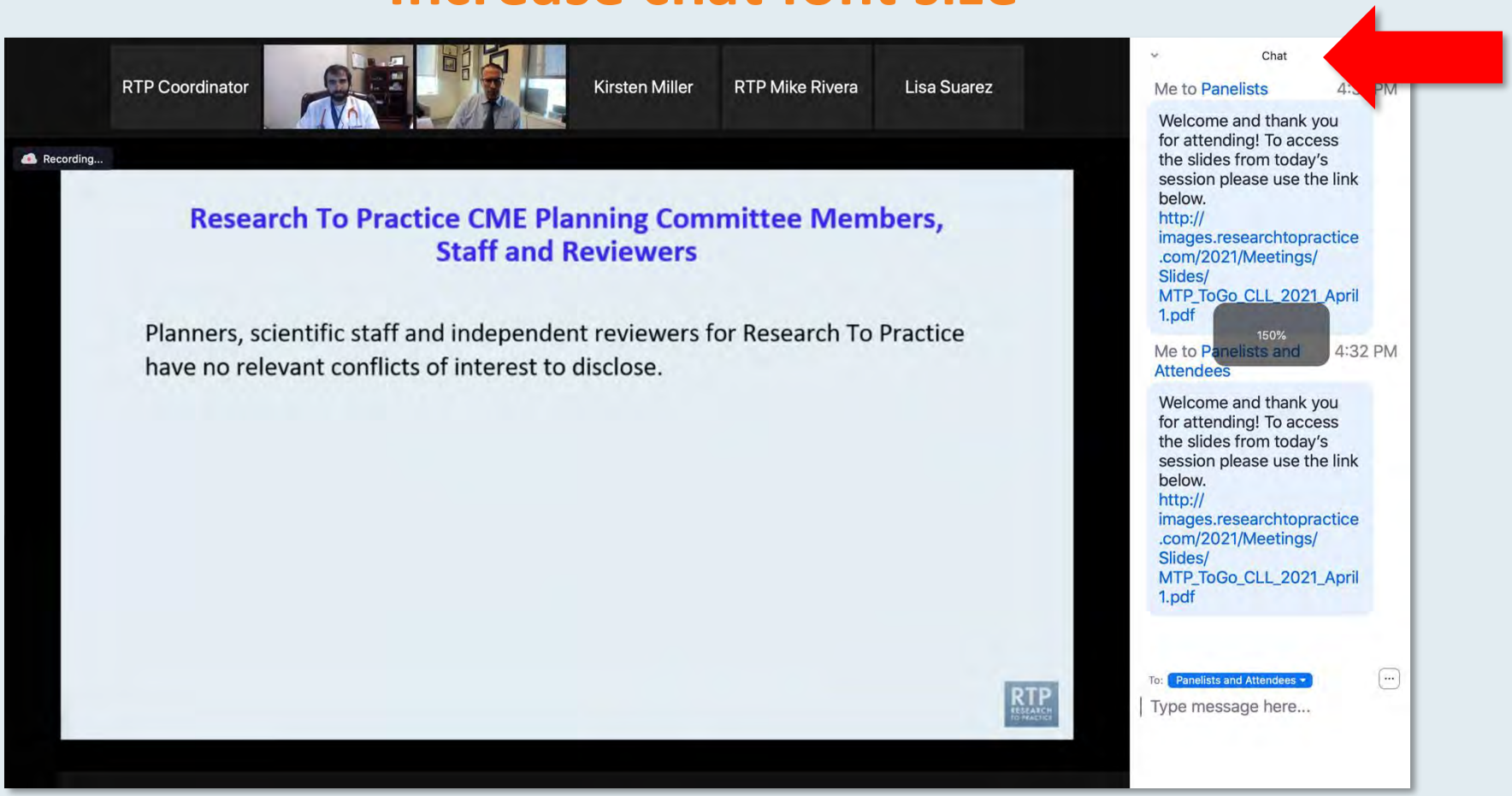

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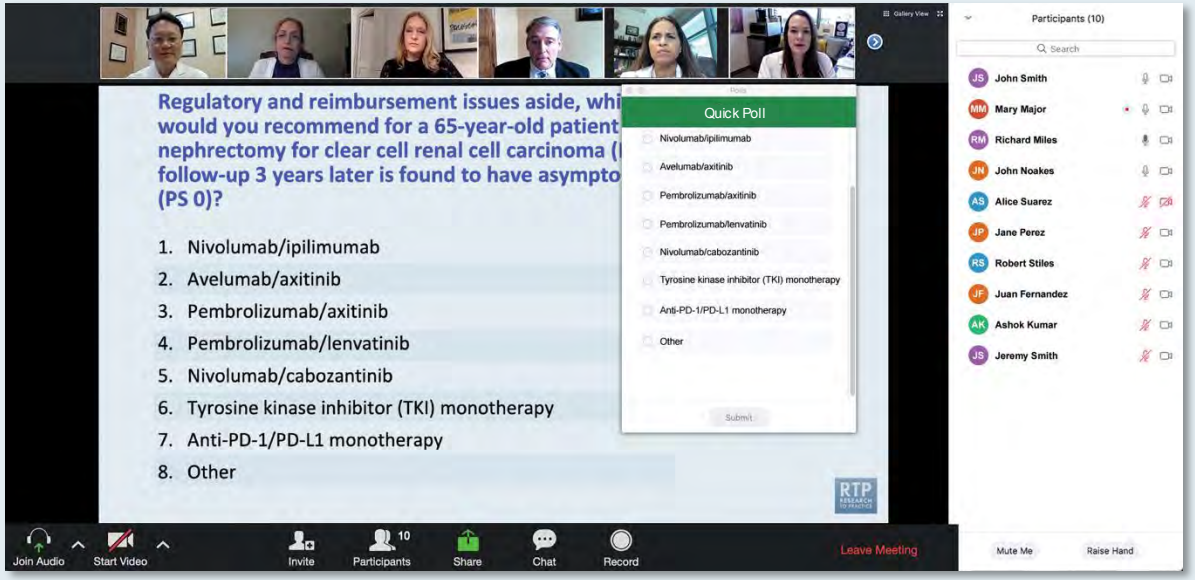

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WITH DR NEIL LOVE

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PROF GIUSEPPE CURIGLIANO
EUROPEAN INSTITUTE OF ONCOLOGY

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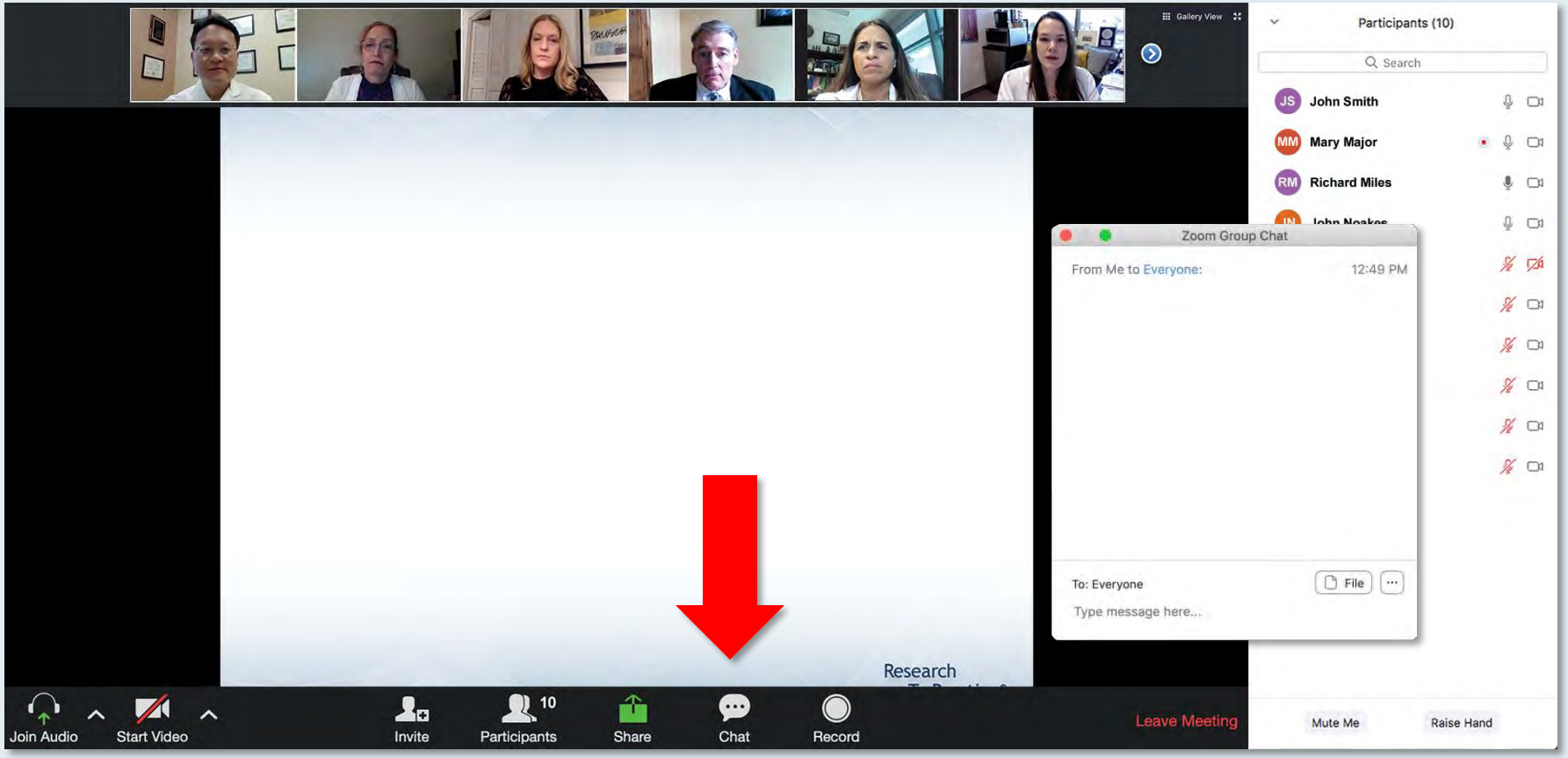

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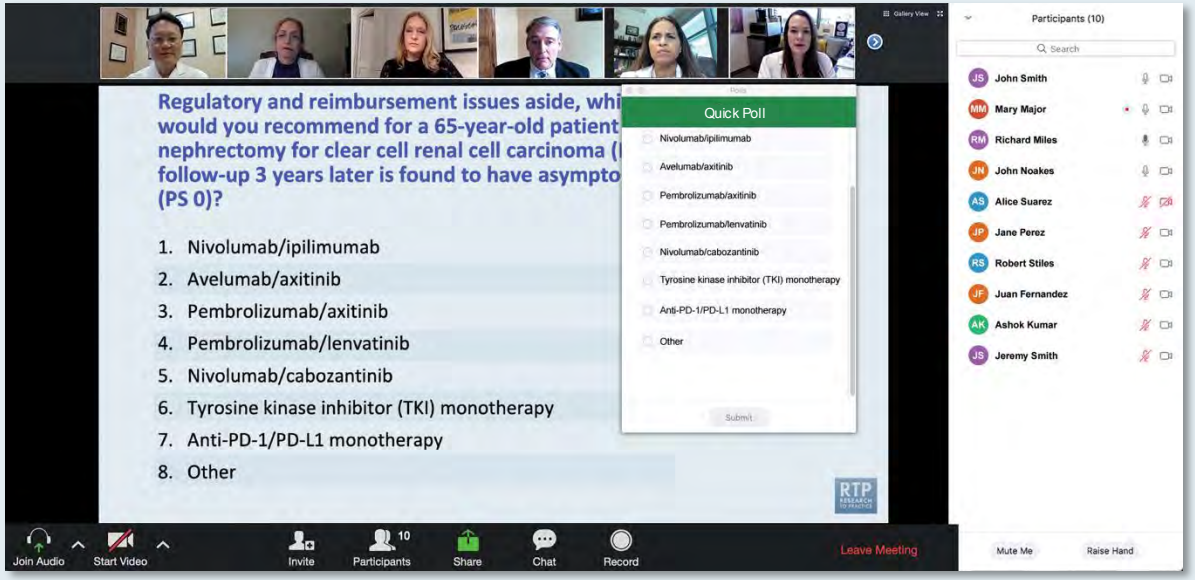

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Module 1: Mechanisms of Resistance to Endocrine Therapy in HR-Positive mBC; Use of Oral Selective Estrogen Receptor Degraders (SERDs) — Dr Kalinsky

Module 2: Ongoing Evaluation of Early Therapeutic Switching for HR-Positive mBC Harboring ESR1 Mutations — Prof Bidard

Module 3: Other Key Datasets and Ongoing Trials in HR-Positive Breast Cancer

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NCCN Guidelines for Invasive Breast Cancer

HR-Positive, HER2-Negative mBC

HR-Positive, HER2-Negative mBC and Postmenopausal Patients or Premenopausal Patients Receiving Ovarian Ablation or Suppression

Setting	Preferred regimens	Other recommended regimens (first and subsequent lines)
First line	Aromatase inhibitor + CDK4/6 inhibitor ▪ Aromatase inhibitor + ribociclib (Category 1) ▪ Aromatase inhibitor + abemaciclib ▪ Aromatase inhibitor + palbociclib	Selective ER downregulator ▪ Fulvestrant ▪ Elacestrant for ESR1-mutated tumors Selective ER downregulator (fulvestrant, Category 1) + nonsteroidal aromatase inhibitor (anastrozole, letrozole) (Category 1) Nonsteroidal aromatase inhibitor ▪ Anastrozole ▪ Letrozole Selective ER modulator ▪ Tamoxifen Steroidal aromatase inactivator ▪ Exemestane
	Fulvestrant + CDK4/6 inhibitor ▪ Fulvestrant + ribociclib (Category 1) ▪ Fulvestrant + abemaciclib (Category 1) ▪ Fulvestrant + palbociclib	
Second line	Fulvestrant + CDK4/6 inhibitor if CDK4/6 inhibitor not previously used (Category 1)	
	Fulvestrant + capivasertib for PIK3CA-, AKT1-mutated or PTEN-altered tumors (Category 1)	
	Alpelisib + fulvestrant for PIK3CA-mutated tumors (Category 1)	
	Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)	

NCCN Clinical Practice Guidelines in Oncology for Breast Cancer. v4.2024. Accessed October 2024.

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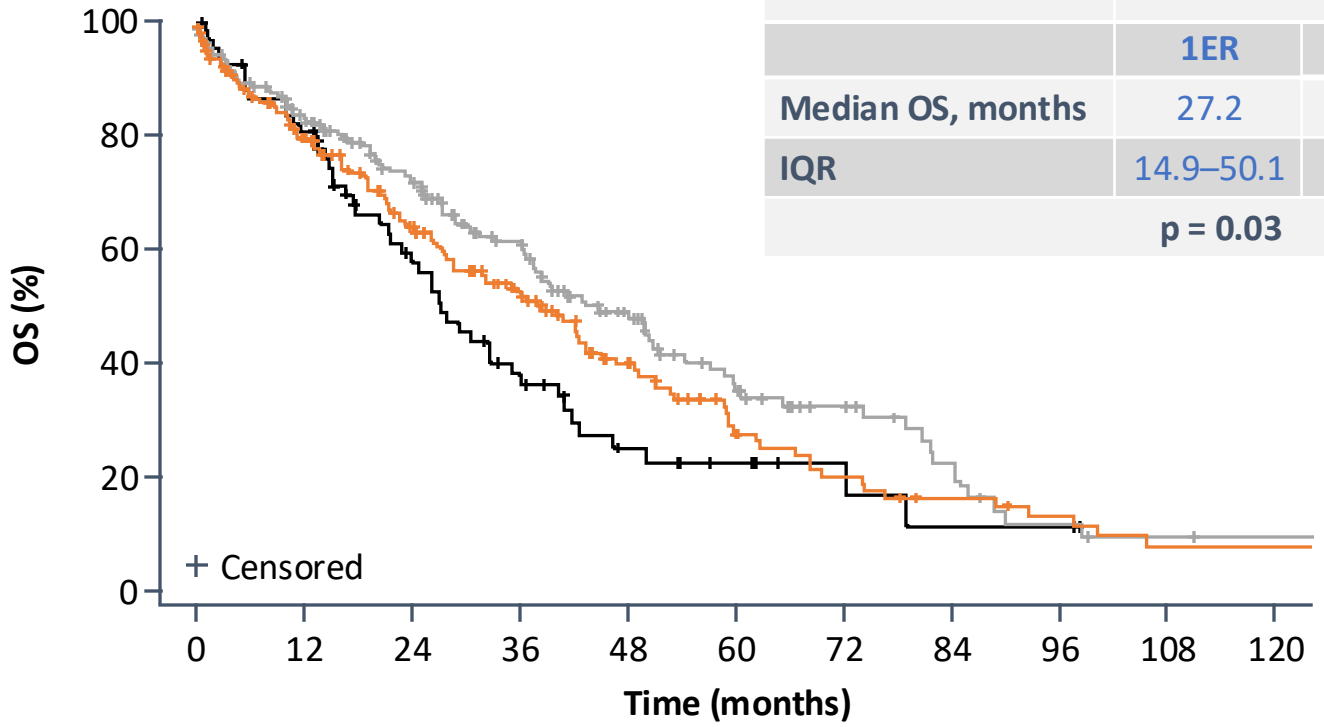
Mechanisms of Resistance to Endocrine Therapy in Hormone Receptor (HR)-Positive Metastatic Breast Cancer (mBC) and Rationale for the Use of Oral Selective Estrogen Receptor Degraders (SERDs) in this Setting

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

Endocrine resistance is associated with poor prognosis in HR+ BC

Patient-level data from four randomised clinical trials* (n = 493 with 1ER, 2ER or ES)†



	Cohort		
	1ER	2ER	ES
Median OS, months	27.2	38.4	43.2
IQR	14.9–50.1	16.3–66.9	20.4–81.8
	p = 0.03		

* N = 9,058; n = 6,612 had HR+, HER2– BC and, of those, n = 493 had distant relapse as the first DFS event.
† Median follow-up from the occurrence of distant relapse was 3.8 years (IQR 1.6–7.5).
1ER, primary endocrine resistance; 2ER, secondary endocrine resistance; BC, breast cancer; DFS, disease-free survival; ES, endocrine sensitive; HR+, hormone receptor-positive; IQR, interquartile range; OS, overall survival.
Lambertini M, *et al. eClinicalMedicine* 2023; **59**:101931.

Results for Pivotal CDK 4/6 Inhibitor Trials

Trial	CDK Inhibitor	Line of Therapy (Endocrine Rx)	Menopausal Status	PFS HR	Statistical Significance	OS HR	Statistical Significance
PALOMA-2[1]	Palbociclib	1st Line/AI	Post	0.56	Yes	0.96	No
MONALEESA-2[2]	Ribociclib	1st Line/AI	Post	0.57	Yes	0.76	Yes
MONALEESA-7[3a]	Ribociclib	1st Line/AI or Tam	Pre/Peri	0.55	Yes	0.70	Yes
MONARCH-3[4]	Abemaciclib	1st Line/AI	Post	0.54	Yes	0.75	No (@IA2)
PALOMA-3[5]	Palbociclib	2nd Line/Fulv	Pre/Post	0.46	Yes	0.81	No
MONARCH-2[6]	Abemaciclib	2nd Line/Fulv	Pre/Post	0.55	Yes	0.78	Yes
MONALEESA-3[7]	Ribociclib	1st /2nd Line/Fulv	Pre/Post	0.59	Yes	0.72	Yes

a. Missing survival data (ie, pts who withdrew consent or were lost to follow-up) and were censored (assumed to be alive) at time of analysis: 13% in palbo+AI arm vs 21% in control arm.
b. 27% of patients in control arm went on to receive a CDK4/6i (24% received palbociclib).
c. PFS/OS data reported for approved AI subset.

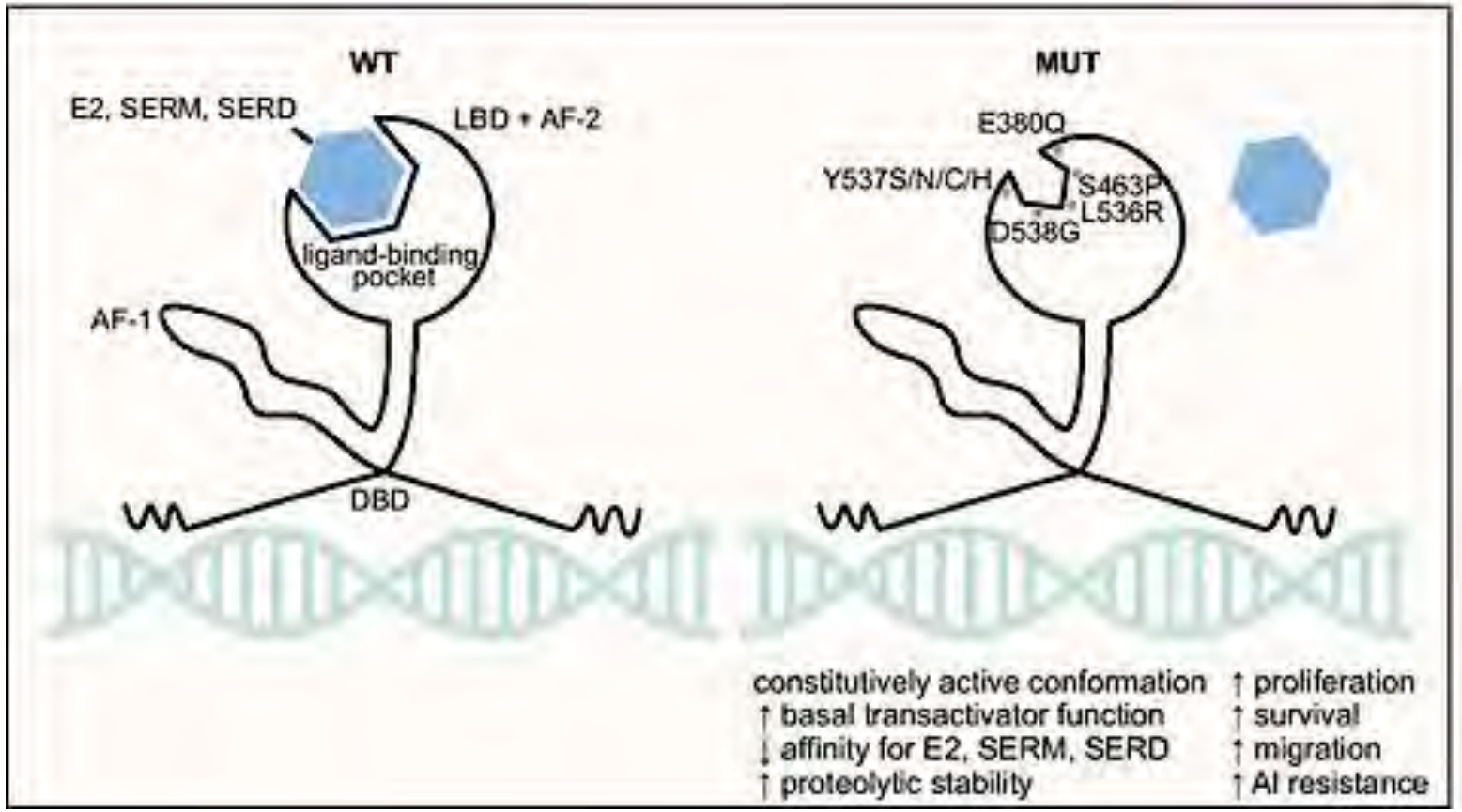
AI indicates aromatase inhibitor; Fulv, fulvestrant; IA2, interim analysis 2; NR, not reported; Rx, therapy.

1. PALOMA-2: Finn R, et al. *N Engl J Med*. 2016;375:1925-1936; Rugo H, et al. *Breast Cancer Res Treat*. 2019;174:719-729. Finn R, et al. ASCO 2022. LBA1003. **2.** MONALEESA-2: Hortobagyi G, et al. *N Engl J Med*. 2016;375:1738-1748; Hortobagyi G, et al. *Ann Oncol*. 2018;29:1541-1547; Hortobagyi G. et al. ESMO 2021. Abstract LBA17_PR. **3.** MONALEESA-7: Tripathy D, et al. *Lancet Oncol*. 2018;19:904-915; Im S-A, et al. *New Engl J Med*. 2019;381:307-316. **4.** MONARCH-3: Goetz M, et al. *J Clin Oncol*. 2017;35:3638-3646; Johnson S, et al. NPJ *Breast Cancer. 2019;5:5.* Goetz MP, et al. ESMO 2022. Abstract LBA 15. **5.** PALOMA-3: Turner NC, et al. *New Engl J Med*. 2015;373:209-219; Cristofanilli M, et al. *Lancet Oncol*. 2016;17:425-439; Turner NC, et al. *New Engl J Med*. 2015;373:1672-1673. **6.** MONARCH-2: Sledge G, et al. *J Clin Oncol*. 2017;35:2875-2884; Sledge G, et al. *JAMA Oncol*. 2020;6:116-124**. 7.** MONALEESA-3: Slamon D, et al. *J Clin Oncol*. 2018;36:2465-2472; Slamon D, et al. *New Engl J Med*. 2020;382:514-524.

Comparison of Paired Post- vs Pre-CDK4/6i Breast Cancer Tumors

Razavi P et al. ASCO 2019. Abstract 1009.

ESR1 mutations in Breast Cancer



Brett JO *et al. Breast Cancer Res* 2021;**23**,85

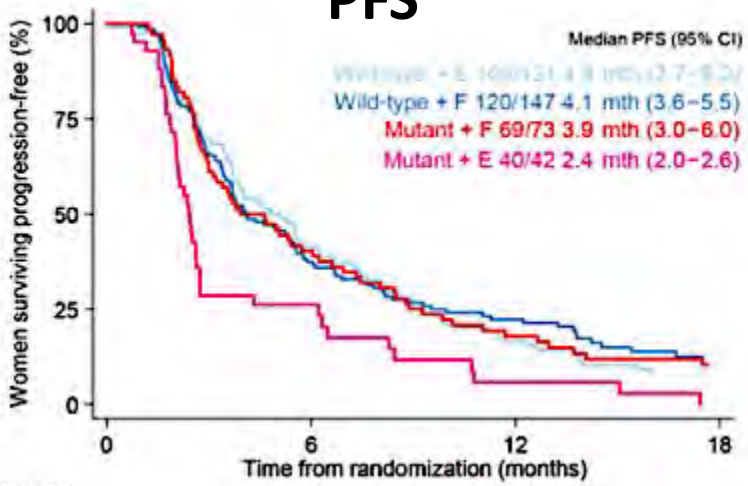
Prevalence of *ESR1* Mutations in Untreated vs Treated ER+/HER2- mBC

Treatment Setting	*ESR1* Mutation Prevalence[1-5]
At Initiation of First-Line ET	~5%
Second-Line	~33%
Third-Line	Up to 40%

1. Jeselsohn R et al. *Clin Cancer Res* 2014;20:1757-1767; **2.** Jeselsohn R et al. *Cancer Cell* 2018;33:173-186; **3.** Allouchery V et al. *Breast Cancer Res* 2018;20:40;
4. Schiavon G et al. Sci Transl Med 2015;7(313):313ra182; **5.** Brett JO et al. *Breast Cancer Res* 2021;23(1):85.

ESR1 Mutations and OS on Fulvestrant vs Exemestane in Advanced HR+ Breast Cancer: A Combined Analysis of the Phase III SoFEA and EFECT

PFS

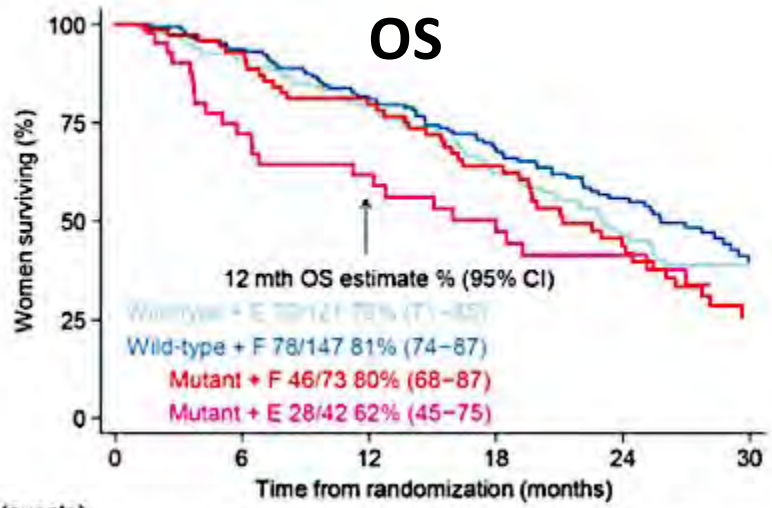


N at risk (events)

Wild-type + E	121	(70)	49	(28)	17	(8)	7
Wild-type + F	147	(87)	50	(19)	25	(10)	8
Mutant + E	42	(31)	9	(7)	2	(2)	0
Mutant + F	73	(43)	29	(16)	12	(5)	6

Figure 2.
PFS in the combined analysis of SoFEA and EFECT by *ESR1* mutation status and treatment. Patients with *ESR1* mutation detected: HR, 0.59; 95% CI, 0.39–0.89; $P = 0.01$. Patients without *ESR1* mutation detected: HR, 1.05, 95% CI, 0.81–1.37; $P = 0.69$. Interaction test $P = 0.02$. E, exemestane; F, fulvestrant; mth, month; mutant, *ESR1* mutation detected; wild-type, *ESR1* mutation not detected.

OS



N at risk (events)

Wild-type + E	121	(11)	109	(14)	93	(19)	68	(15)	37	(6)	21
Wild-type + F	147	(9)	134	(18)	113	(17)	89	(15)	59	(13)	26
Mutant + E	42	(11)	28	(4)	22	(4)	17	(3)	11	(2)	6
Mutant + F	73	(5)	64	(9)	52	(10)	38	(11)	23	(8)	9

Figure 3.
OS in the combined analysis of SoFEA and EFECT by *ESR1* mutation status and treatment. Patients with *ESR1* mutation detected: restricted mean survival analysis $P = 0.04$. Patients without *ESR1* mutation detected: restricted mean survival analysis $P = 0.69$. E, exemestane; F, fulvestrant; mth, month; mutant, *ESR1* mutation detected; wild-type, *ESR1* not detected.

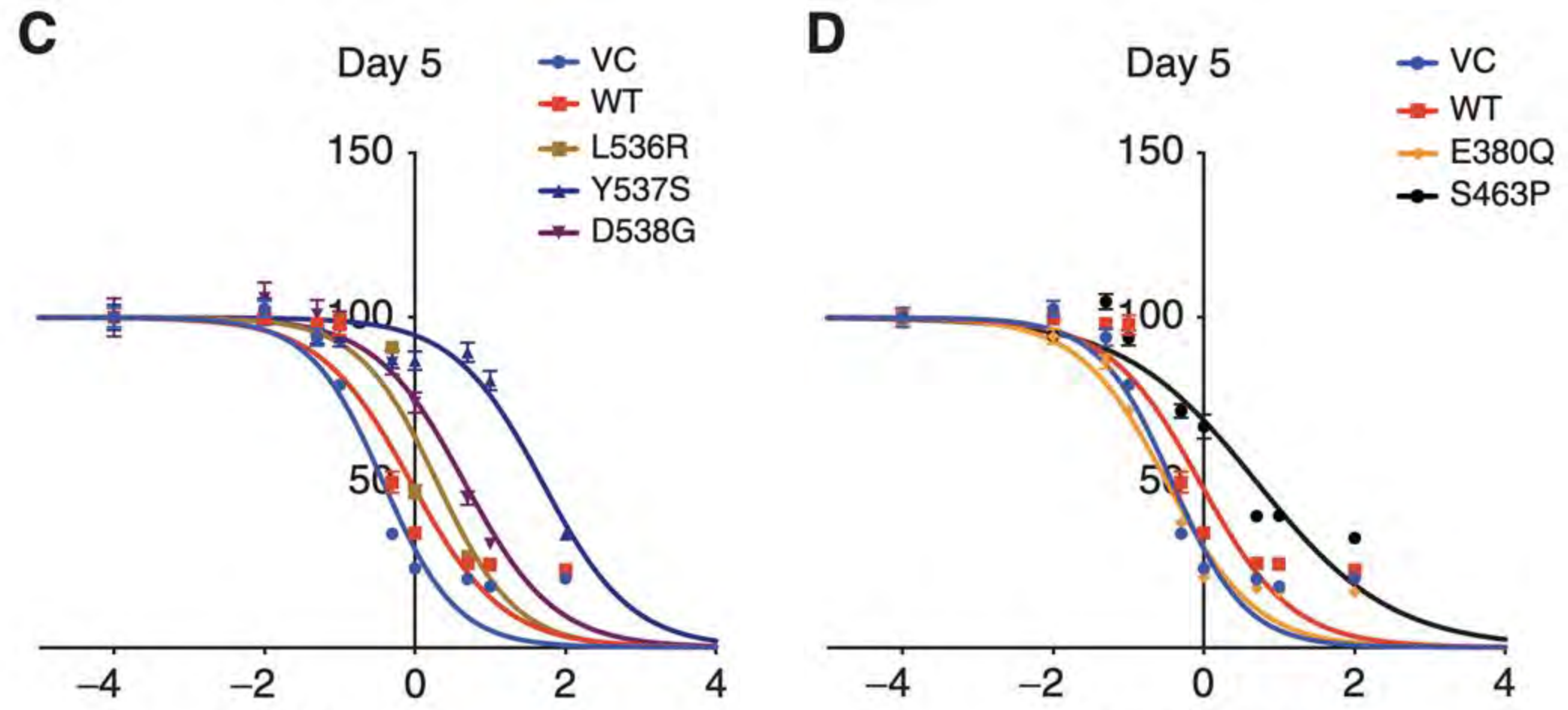
Turner N, et al. Clin Cancer Res 2020;26:5172–7

ESR1 Mutations

Trial	Study treatment	Patient population	Patients (n substudy/ total N on trial)	ESR1 mutation frequency
MONALEESA-2[1]	Letrozole ± Ribociclib	1st line ER+ MBC	494/668	4.0%
BOLERO-2[2]	Exemestane ± Everolimus	ER+ MBC after PD on ET	541/724	28.8%
FERGI[3]	Fulvestrant ± Pictilisib	ER+ MBC after PD on ET	153/168	37.3%
PALOMA-3[4]	Fulvestrant ± Palbociclib	ER+ MBC after PD on ET	360/521	25.3%

1. Hortobagyi GN et al. Ann Oncol. 2018;29:1541-1547. 2. Chandarlapaty S et al. JAMA Oncol. 2016;2:1310-1315. 3. Spoerke JM et al. Nat Commun. 2016;7:11579. 4. Fribbens C et al. J Clin Oncol. 2016;34:2961-2968.

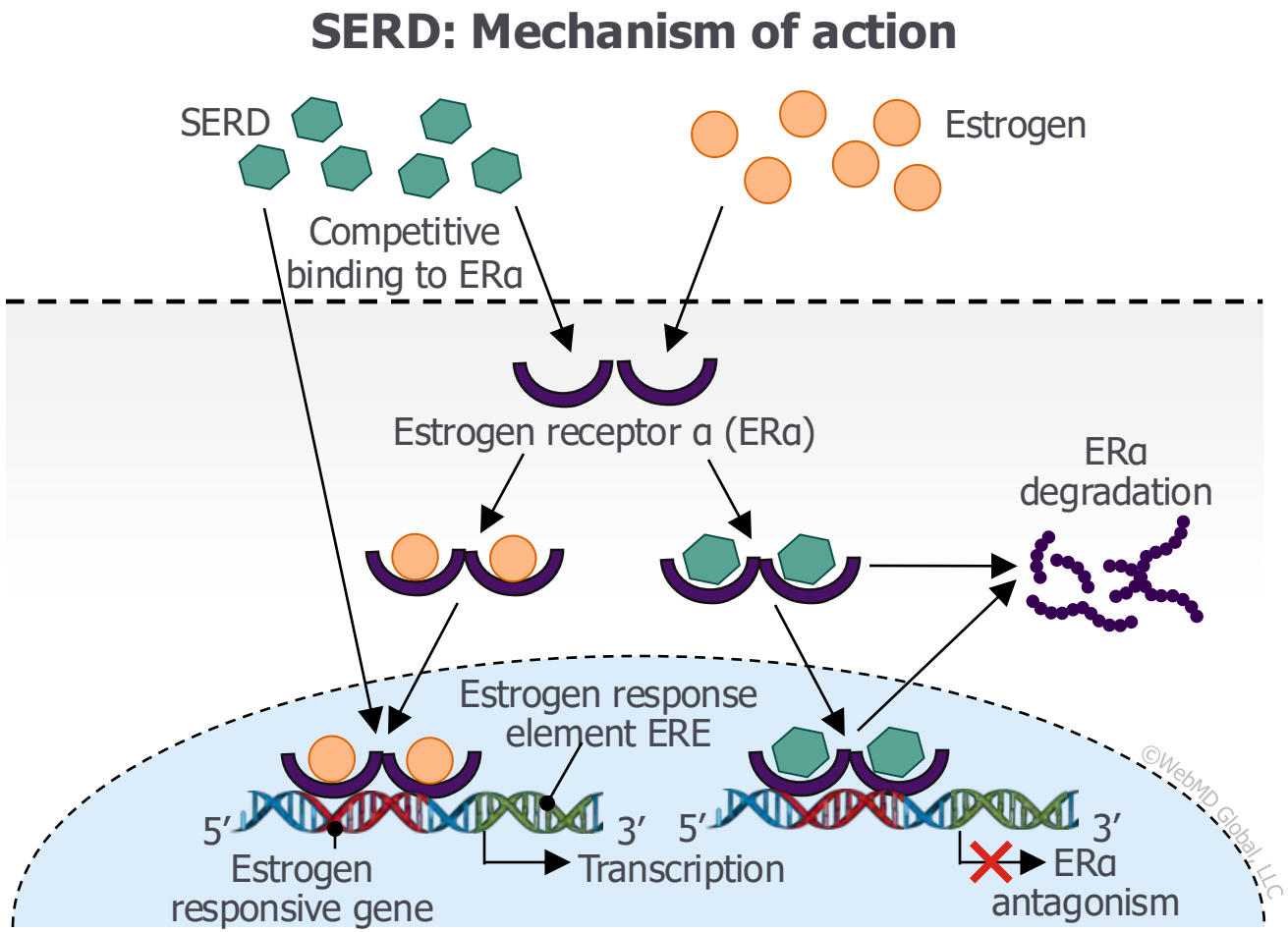
In Vivo Activity of Fulvestrant Against Different ESR1m

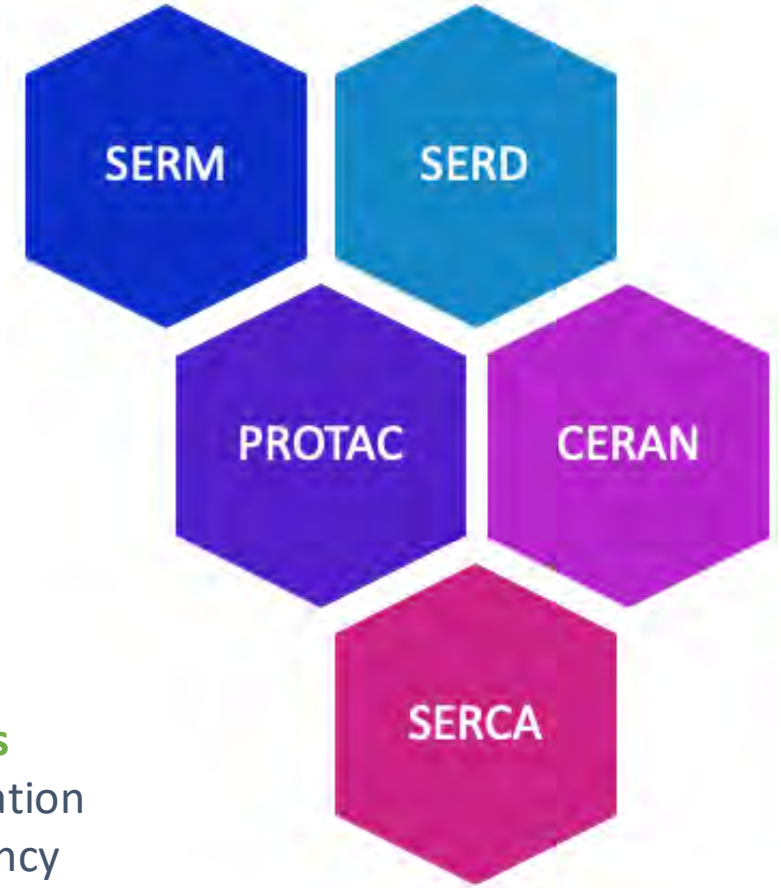


Y537S mutants required highest IC_{50} (55-fold higher than WT)

Toy W, et al. *Cancer Discov* 2017;7:277-87

Novel endocrine therapies may address endocrine resistance in MBC



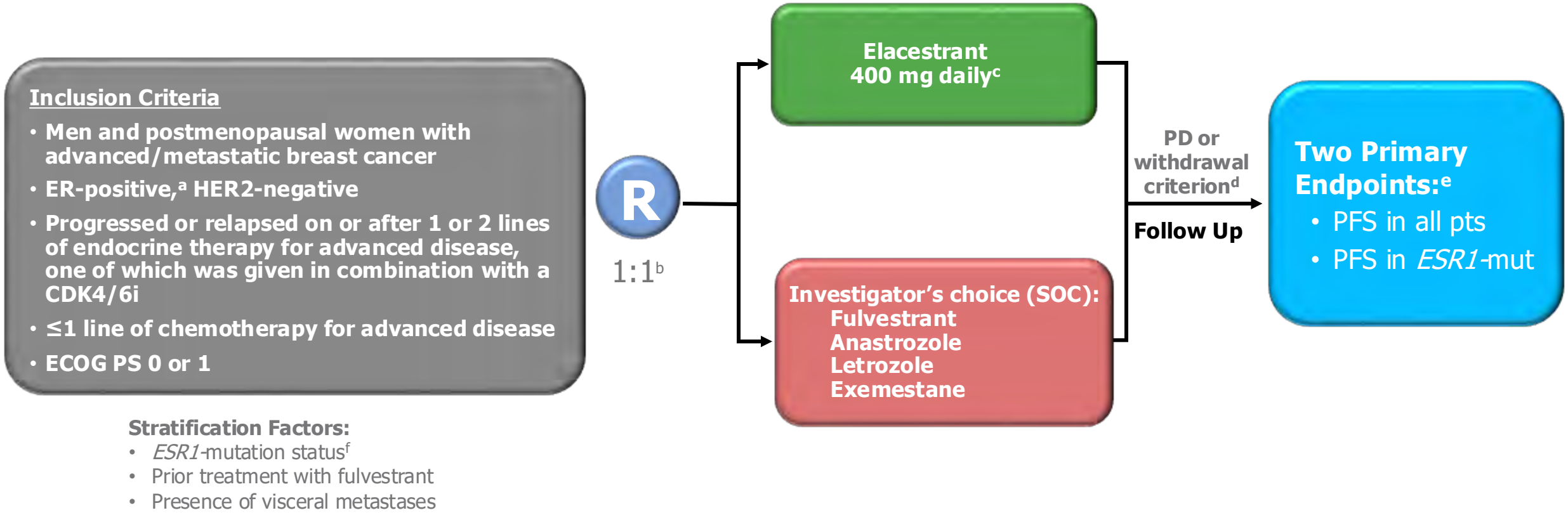


Key advantages

- Oral formulation
- Higher potency
- Activity in ESR1 mutant MBC
- Activity in post-ET and CDK4/6i treated pts

Hernando et al, Int J Mol Sci 2021; slide adapted from Erika Hamilton

EMERALD Phase 3 Study Design

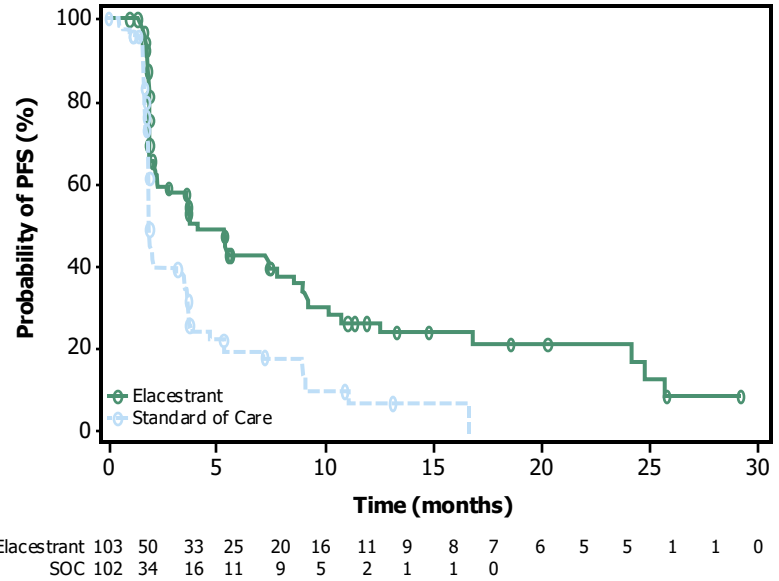


[a]Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry; [b]Recruitment from February 2019 to October 2020; [c]Protocol-defined dose reductions permitted; [d]Restaging CT scans every 8 weeks; [e]Blinded Independent Central Review; [f]*ESR1*-mutation status was determined by ctDNA analysis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

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

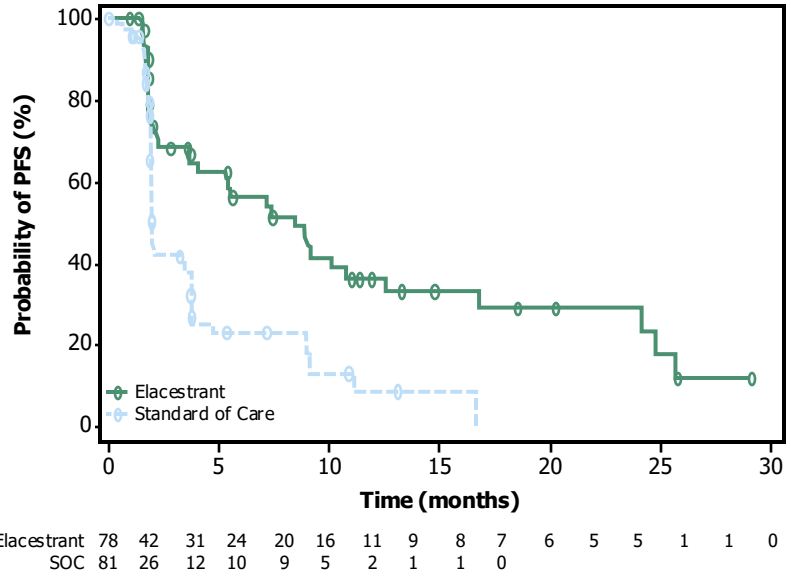
Patients with *ESR1*-mut Tumors: PFS by Duration of CDK4/6i

At least 6 mo CDK4/6i



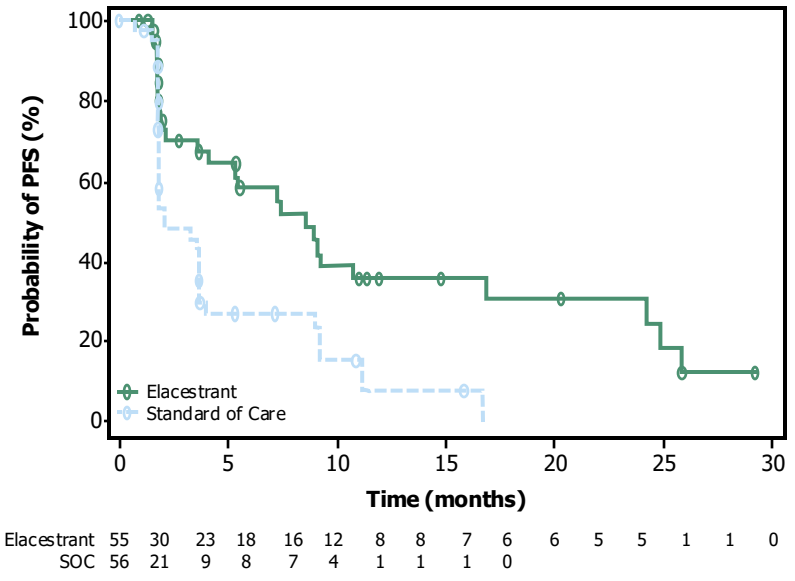
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

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)	

Various oral SERDs are being investigated on the horizon, pionERA is the only study addressing specific endocrine resistance and building on learnings from ESR1 mutation unmet need from previous studies

SERD	giredestrant	elacestrant	camizestrant	imlunestrant	amcenestrant* (discont.)
mBC					
1L PhIII +CDKi	**persevERA BC**[1] gired vs. let (+palbo) **pionERA BC**† gired vs. fulv (+CDKi) in ET-resistant	--	**SERENA-4**[9] cami vs. ana (+palbo) **SERENA-6**[10] cami vs. AI (+palbo/abema) in emerging *ESR1*m	--	**AMEERA-5**[17] amce vs. let (+palbo)
2L PhII–III	**acelERA BC**[2] PhII gired vs. PCE **evERA BC**[3] PhIII gired vs. PCE (+evero)	**EMERALD**[6] PhIII ela vs. PCE	**SERENA-2**[11] PhII cami (2 dose arms) vs. fulv	**EMBER-3**[14] PhIII imlu vs. PCE vs imlu+abema	**AMEERA-3**[18] amce vs. PCE
eBC					
Neoadj / WoO PhI–II	**coopERA BC**[4] PhII gired vs. ana (+palbo)	**ELIPSE**[7] PhI ela single-arm	**SERENA-3**[12] PhII cami (3 dose arms)	**EMBER-2**[15] PhI imlu (3 dose arms)	**AMEERA-4**[19] PhII amce vs. let **I-SPY EOP**[20] PhII amce+/-abema
Adjuvant PhIII	**lidERA BC**[5] gired vs. PCE, upfront	**TREAT**[8] ela vs. PCE, switch in rising ctDNA	**CAMBRIA-1**[13] cami vs PCE, switch	**EMBER-4**[16] imlu vs. PCE, switch	**AMEERA-6**[21] amce vs. tam, switch

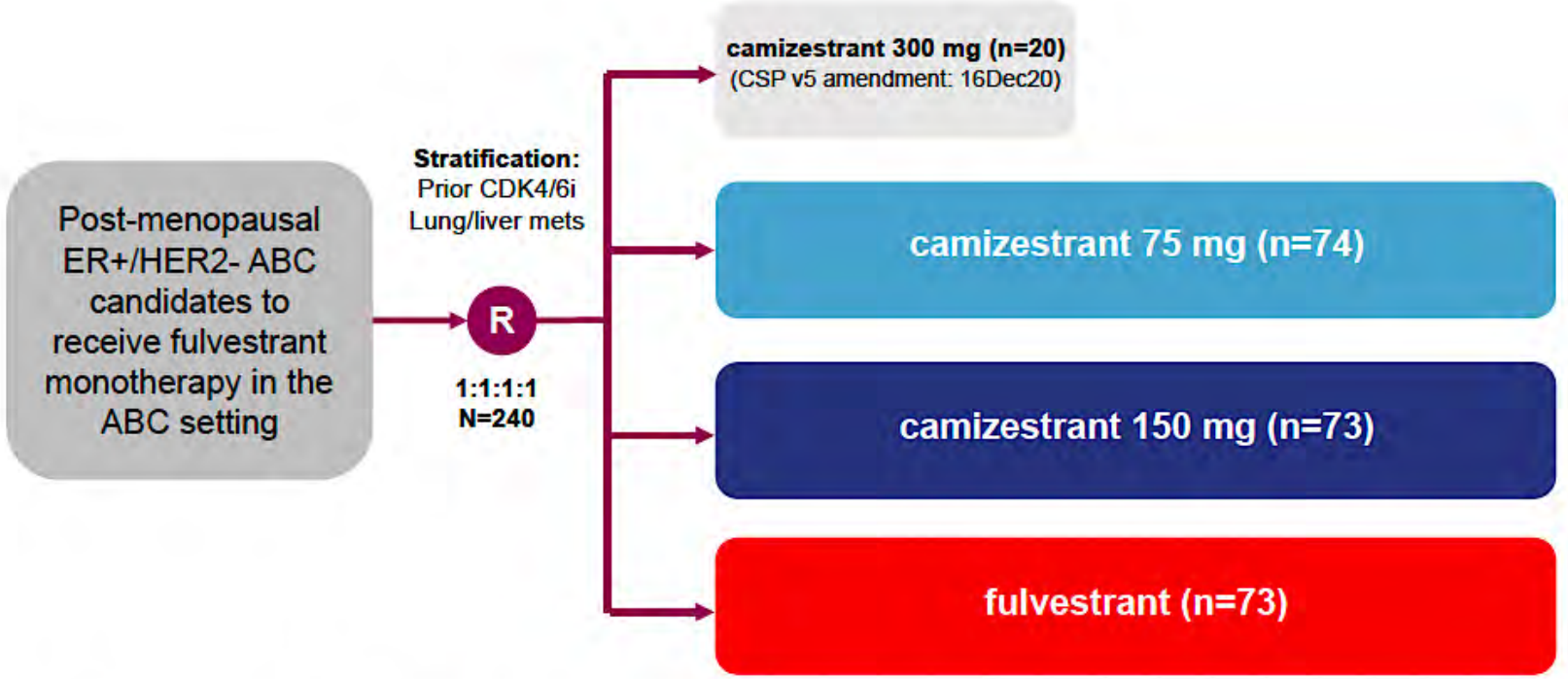
* Discontinued clinical development of amcenestrant.
† Planned for 2023.
AI, aromatase inhibitor; amce, amcenestrant; ana, anastrozole; cami, camizestrant; CDKi, cyclin-dependent kinase inhibitor; ela, elacestrant; fulv, fulvestrant; gired, giredestrant; imlu, imlunestrant; let, letrozole; PCE: physician's choice endocrine therapy; tam, tamoxifen; WoO, window of opportunity. References in slide notes.

Questions?

SERENA-2 Phase II Study 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

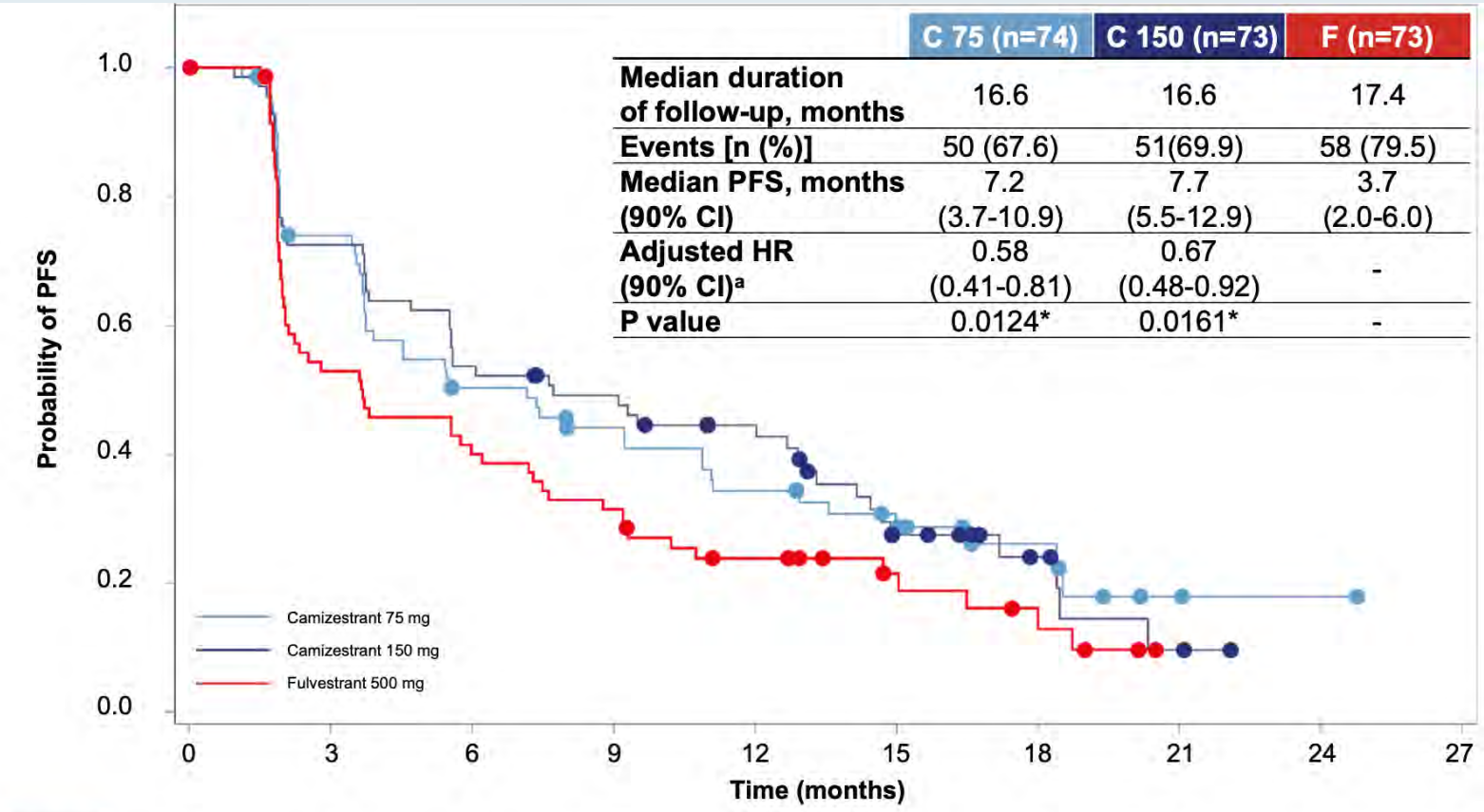


- **Primary endpoint:** PFS (investigator assessment*)
- **Secondary endpoints:** CBR24, ORR, OS, safety
- **Translational endpoints:** serial ctDNA analysis including *ESR1*m, serial CTCs analysis

ET = endocrine therapy; ABC = advanced breast cancer; CT = chemotherapy; PFS = progression-free survival; CBR24 = clinical benefit rate at 24 weeks; ORR = objective response rate; OS = overall survival; ctDNA = circulating tumor DNA; CTCs = circulating tumor cells

Oliveira M et al. San Antonio Breast Cancer Symposium 2022;Abstract GS3-02.

Phase II SERENA-2 Trial: PFS by Investigator Assessment (Primary Endpoint)



	C 75 (n=74)	C 150 (n=73)	F (n=73)
Median duration of follow-up, months	16.6	16.6	17.4
Events [n (%)]	50 (67.6)	51(69.9)	58 (79.5)
Median PFS, months (90% CI)	7.2 (3.7-10.9)	7.7 (5.5-12.9)	3.7 (2.0-6.0)
Adjusted HR (90% CI)[a]	0.58 (0.41-0.81)	0.67 (0.48-0.92)	-
P value	0.0124*	0.0161*	-

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

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

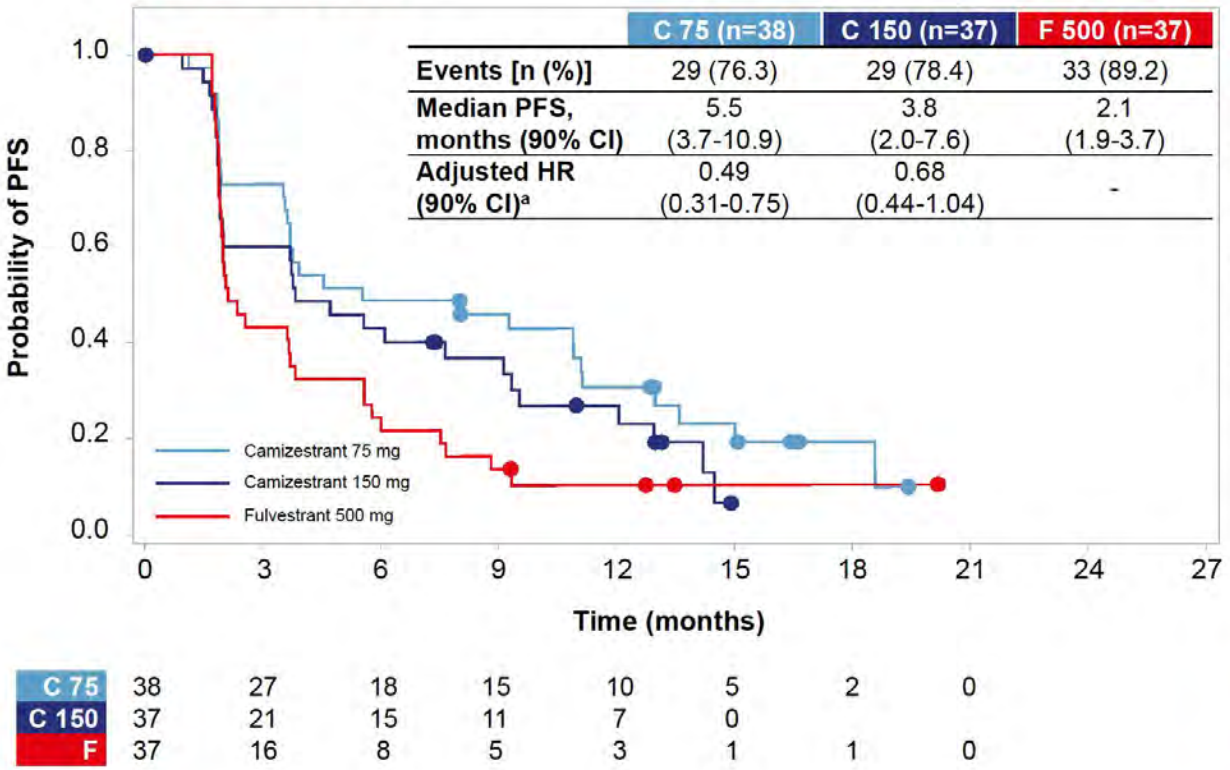
CDK4/6i: CDK4/6 inhibitor; CI: confidence interval; HR: hazard ratio; PFS: progression-free survival

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

Oliveira M et al. San Antonio Breast Cancer Symposium 2022;Abstract GS3-02.

Phase II SERENA-2 Trial: PFS by Prior CDK4/6 Inhibitor (CDK4/6i)

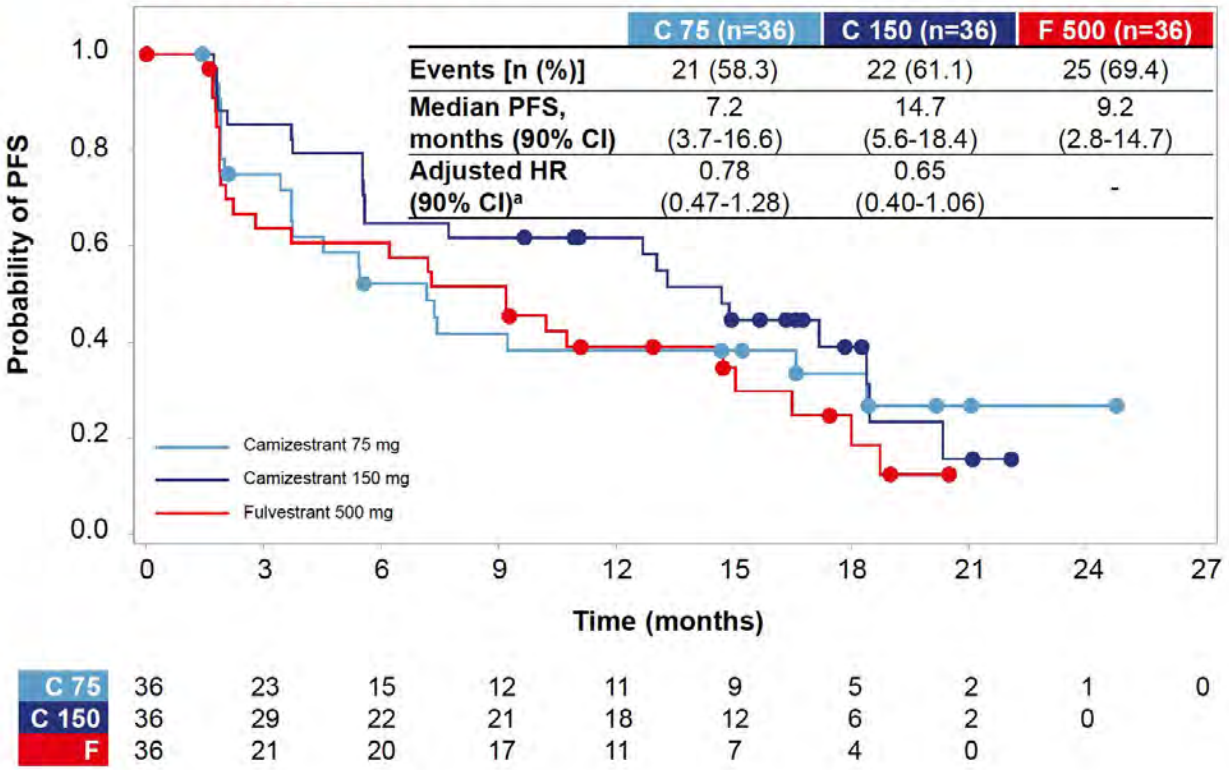
Prior CDK4/6i



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

C 75	38	27	18	15	10	5	2	0
C 150	37	21	15	11	7	0		
F	37	16	8	5	3	1	1	0

No prior CDK4/6i

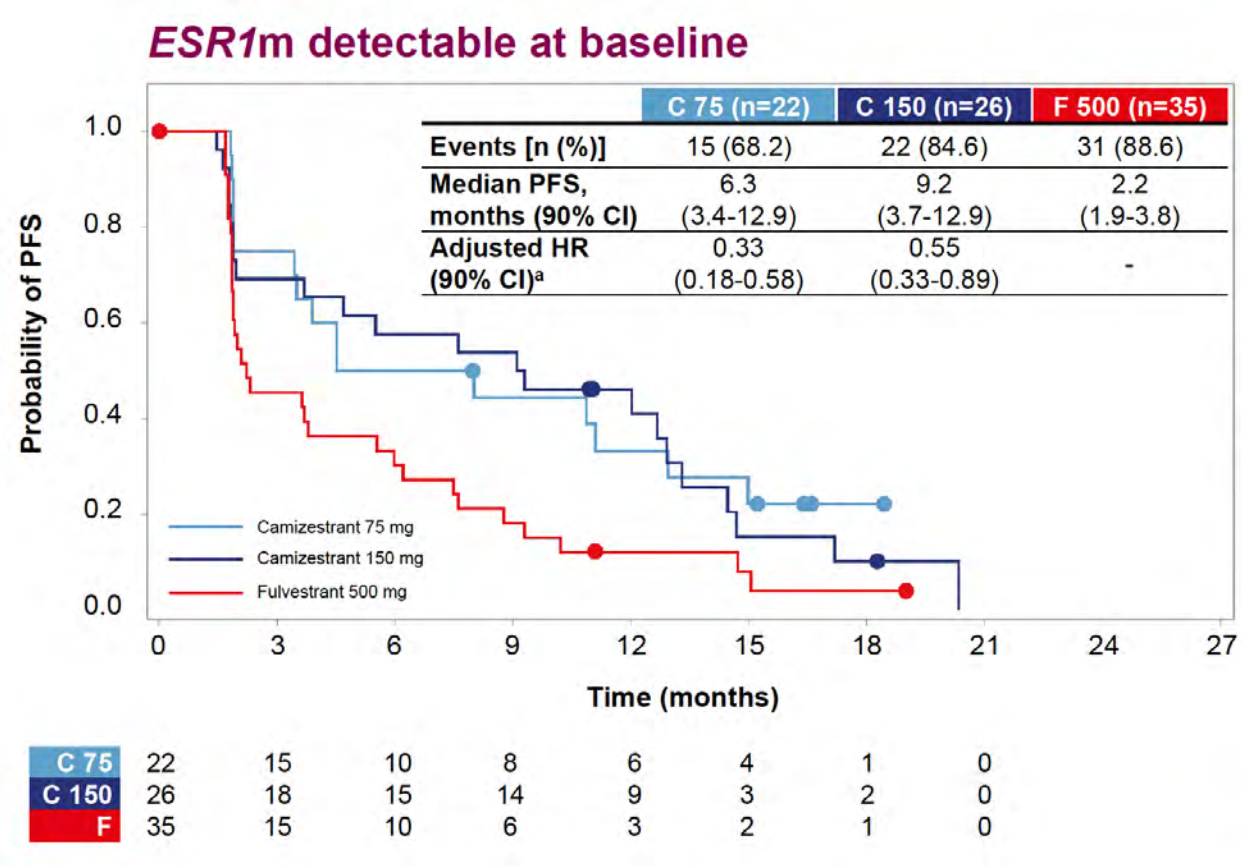


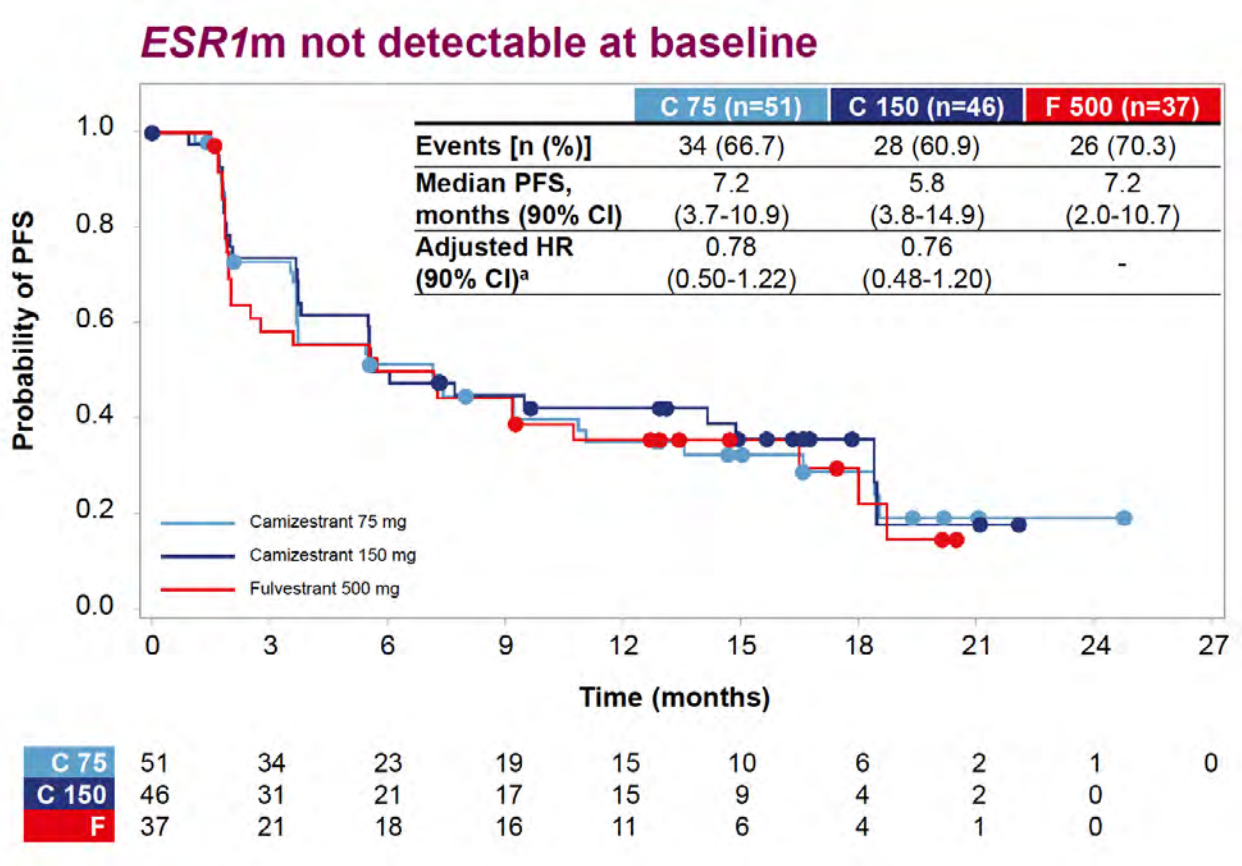
	C 75 (n=36)	C 150 (n=36)	F 500 (n=36)
Events [n (%)]	21 (58.3)	22 (61.1)	25 (69.4)
Median PFS, months (90% CI)	7.2 (3.7-16.6)	14.7 (5.6-18.4)	9.2 (2.8-14.7)
Adjusted HR (90% CI)[a]	0.78 (0.47-1.28)	0.65 (0.40-1.06)	-

C 75	36	23	15	12	11	9	5	2	1	0
C 150	36	29	22	21	18	12	6	2	0	
F	36	21	20	17	11	7	4	0		

Oliveira M et al. San Antonio Breast Cancer Symposium 2022;Abstract GS3-02.

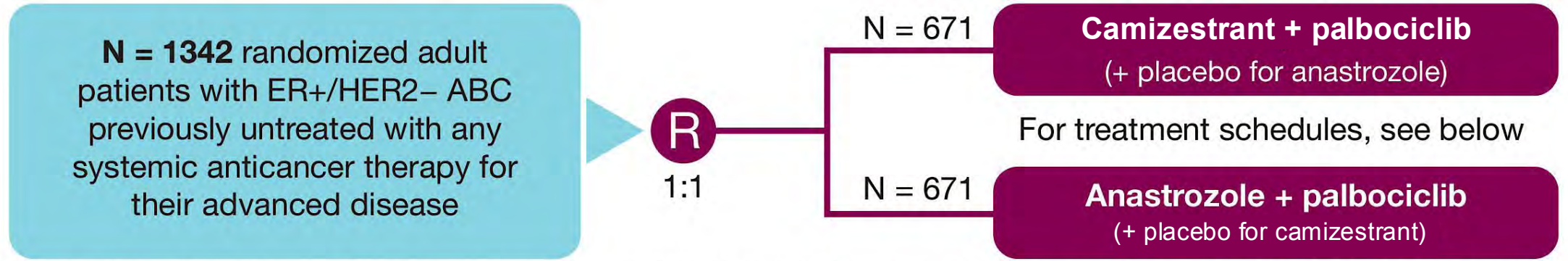
Phase II SERENA-2 Trial: PFS by Detectable ESR1





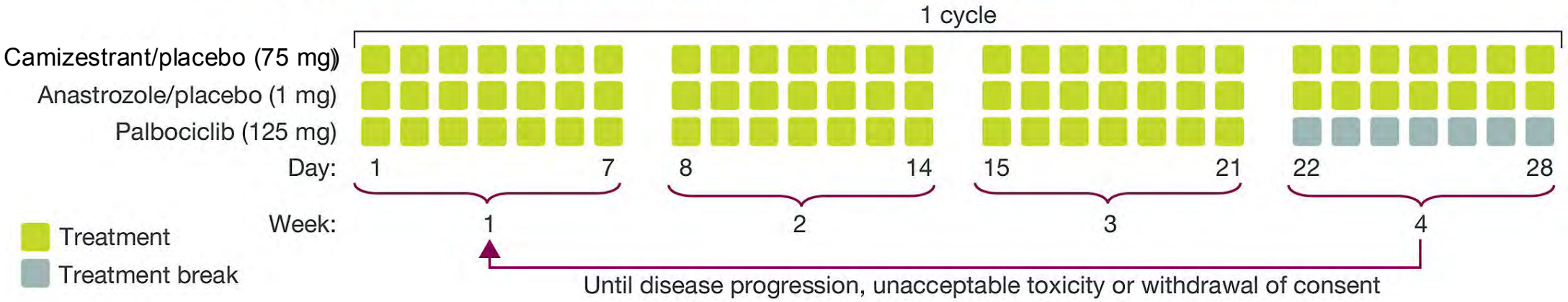
Oliveira M et al. San Antonio Breast Cancer Symposium 2022;Abstract GS3-02.

SERENA-4 Phase III Study Design



Pre-/peri-menopausal women or male participants must receive a concurrent monthly luteinizing hormone-releasing hormone agonist (goserelin or leuprorelin), as medically applicable.
ABC, advanced breast cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; R, randomization.

Drugs will be administered orally, once daily following the schedule detailed below



Im SA et al. ASCO 2021;Abstract TPS1101.

Rapid Recommendation Update

Recommendation

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
High	Strong

- Routine testing for emergence of *ESR1* mutations at recurrence or progression on ET (with or without CDK4/6 inhibitor) in pts with ER-positive, HER2-negative MBC.

  Testing with a CLIA-certified assay should be performed on blood or tissue obtained at the time of progression. Blood-based ctDNA is preferred owing to greater sensitivity.

  Pts whose tumor or ctDNA tests remain *ESR1* wildtype may warrant retesting at subsequent progression(s) to determine if an *ESR1* mutation has arisen.

INAVO120 study design

Key eligibility criteria

Enrichment of patients with poor prognosis:

- ***PIK3CA*-mutated, HR+, HER2- ABC** by central ctDNA* or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**

- **No prior therapy for ABC**
- **Fasting glucose <126 mg/dL and HbA_{1C} <6.0%**

Enrolment period: December 2019 to September 2023

N=325

R 1:1

Inavolisib (9 mg QD PO) + palbociclib (125 mg PO QD D1–D21) + fulvestrant (500 mg C1D1/15 and Q4W)**

Placebo (PO QD) + palbociclib (125 mg PO QD D1–D21) + fulvestrant (500 mg C1D1/15 and Q4W)**

Until PD or toxicity

SURVIVAL FOLLOW-UP

Stratification factors:

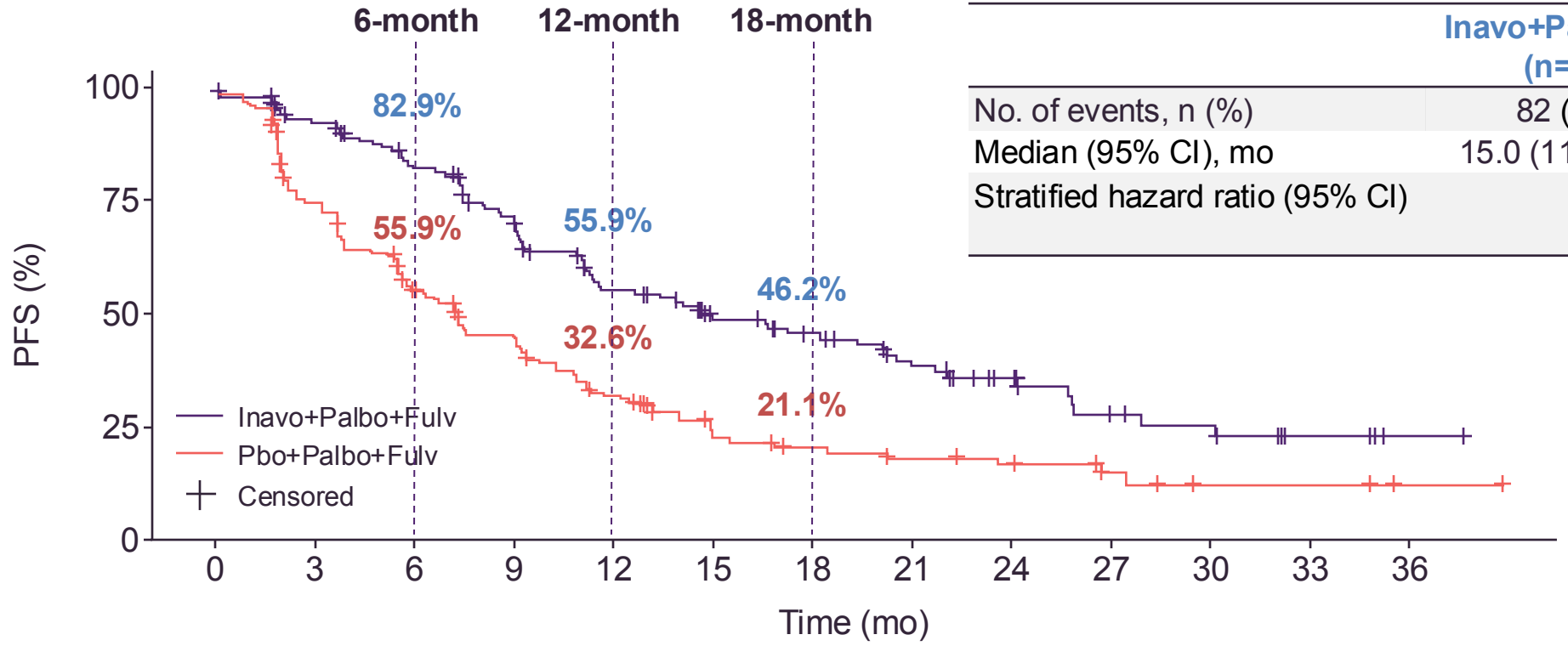
- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

Endpoints

- Primary: PFS by Investigator
- Secondary: OS‡, ORR, BOR, CBR, DOR, PROs

* Central testing for *PIK3CA* mutations was done on ctDNA using FoundationOne®Liquid (Foundation Medicine). In China, the central ctDNA test was the PredicineCARE NGS assay (Huidu). † Defined per 4th European School of Oncology (ESO)–European Society for Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer.[1] Primary: relapse while on the first 2 years of adjuvant ET; Secondary: relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET. ‡ OS testing only if PFS is positive; interim OS analysis at primary PFS analysis;
** Pre-menopausal women received ovarian suppression. ctDNA, circulating tumor DNA; R, randomized. 1. Cardoso F, *et al. Ann Oncol* 2018;**29:**1634–1657.

Primary endpoint: PFS (investigator-assessed)



	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), mo	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Stratified hazard ratio (95% CI)	**0.43 (0.32, 0.59) p<0.0001**	

Patients at risk:

Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

Median follow-up:
21.3 months

CCOD: 29th September 2023

CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

Novel endocrine therapy, including oral SERDs, will continue to have important role in HR+ mBC

Case 1: Second-Line Treatment of HR-Positive/HER2-Negative *ESR1*-Mutated Metastatic Breast Cancer

Dr Kalinsky – Case Presentation

- Patient is a 42-yo **premenopausal** healthy female who is diagnosed with a right breast invasive ductal carcinoma, grade 2, ER+ 95% PR+ 80% HER2 1+
- No prior breast imaging until it was T3N2
- Staging and lung biopsy confirmed **bone and lung metastases**
- Her performance status is excellent
- She has **moderate back pain** from metastases
- Hereditary Genetic Testing: no pathogenic variants

Dr Kalinsky – Case Presentation (Continued)

- Patient undergoes TAH/BSO
- She receives ribociclib plus AI
- After 34 mo of therapy, the patient has progressive disease
- She undergoes ctDNA testing: biomarker testing reveals a pathogenic *ESR1* Y537S mutation

What therapy would you recommend next?

1. Alpelisib + fulvestrant
2. Chemotherapy
3. Capivasertib + fulvestrant
4. Elacestrant
5. Switch CDK4/6 inhibitor + AI combination
6. Trastuzumab Deruxtecan
7. Sacituzumab Govitecan

Dr Kalinsky – Case Presentation (Continued)

- Pt started single agent elacestrant and is tolerating

Agenda

Introduction: Confronting Metastatic Breast Cancer (mBC)

Module 1: Mechanisms of Resistance to Endocrine Therapy in HR-Positive mBC; Use of Oral Selective Estrogen Receptor Degraders (SERDs) — Dr Kalinsky

Module 2: Ongoing Evaluation of Early Therapeutic Switching for HR-Positive mBC Harboring ESR1 Mutations — Prof Bidard

Module 3: Other Key Datasets and Ongoing Trials in HR-Positive Breast Cancer

Early Therapeutic Switching in Patients Found to Harbor *ESR1* Mutations

Francois-Clement Bidard

Curie Institute & Versailles University, France

Extending the first line

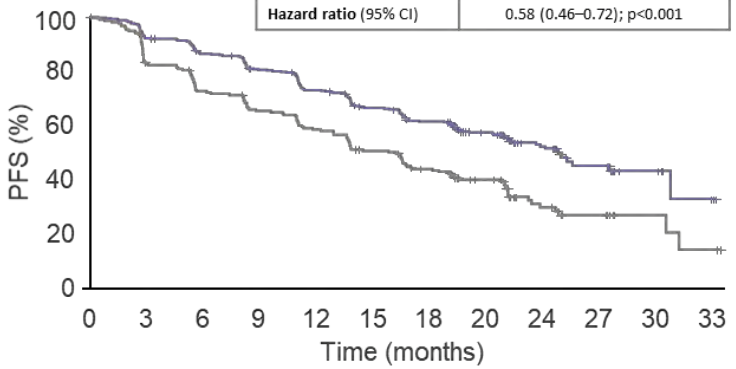
In ER+ HER2- endocrine sensitive mBC, AI+CDK4/6i is the current standard of care in L1

Longest PFS ever observed in mBC (~ 24 months mPFS)

PALOMA-2

PFS

	Palbociclib + letrozole	Placebo + letrozole
Median PFS, months	24.8	14.5
Hazard ratio (95% CI)	0.58 (0.46–0.72); p<0.001	



Number at risk

Palbociclib + letrozole
444 395 360 328 295 263 238 154 69 29 10 2

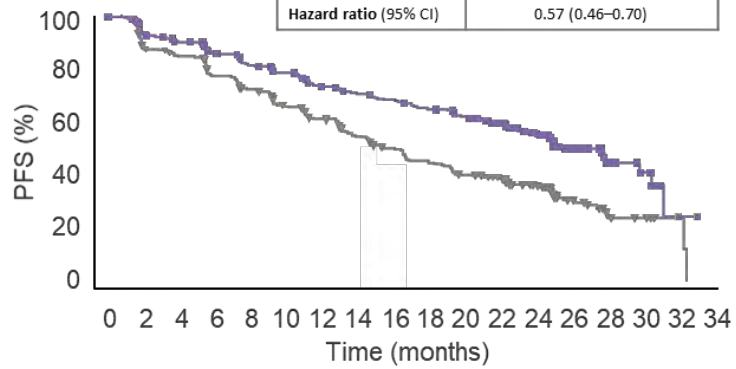
Placebo + letrozole
222 171 148 131 116 98 81 54 22 12 4 2

Neutropenia was the most frequently reported any-grade AE with palbociclib + letrozole vs. placebo + letrozole (81.8% vs. 6.3%)*[2]

MONALEESA-2

PFS

	Ribociclib + letrozole	Placebo + letrozole
Median PFS, months	25.3	16.0
Hazard ratio (95% CI)	0.57 (0.46–0.70)	



Number at risk

Ribociclib + letrozole
334 294 277 257 240 227 207 196 188 176 164 132 97 46 17 11 1 0

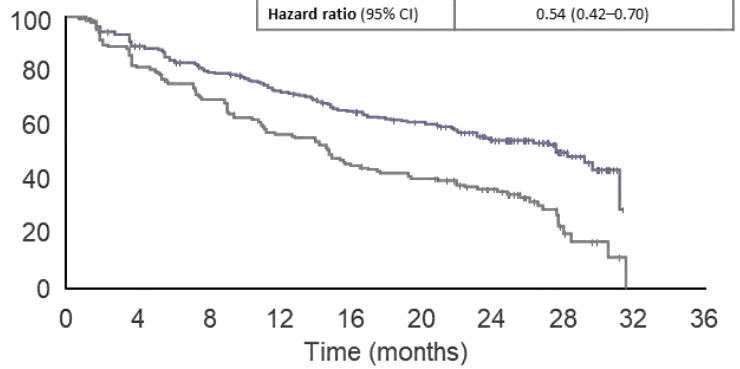
Placebo + letrozole
334 279 265 239 219 196 179 156 138 124 110 93 63 34 10 7 2 0

The most common Grade ≥3 AEs in the ribociclib arm vs. the placebo arm included neutropenia (59.3% vs. 0.9%), leukopenia (21.0% vs. 0.6%), hypertension (9.9% vs. 10.9%) and increased ALT (9.3% vs. 1.2%)[4]

MONARCH-3

PFS

	Abemaciclib + ANA/LET	Placebo + ANA/LET
Median PFS, months	28.2	14.8
Hazard ratio (95% CI)	0.54 (0.42–0.70)	



Number at risk

Abemaciclib + anastrozole/letrozole
328 272 236 208 181 164 106 40 0 0

Placebo + anastrozole/letrozole
165 126 105 84 66 58 42 7 0 0

The most frequent Grade ≥3 AEs in the abemaciclib arm vs. placebo arm were neutropenia (23.9% vs. 1.2%), diarrhoea (9.5% vs. 1.2%) and leukopenia (8.6% vs. 0.6%)

with an overall **very good tolerability**

Extending the first line

In ER+ HER2- endocrine sensitive mBC, AI+CDK4/6i is the current standard of care in L1

Longest PFS ever observed in mBC (~ 24 months mPFS)

but

Acquired resistance eventually appears in all patients ➔ disease progression

[a] Andre, NEJM 2019 ; [b] Rugo, Lancet Oncol 2021

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PFS of subsequent lines of therapy shortened by the prior use of CDK4/6i

e.g. : fulvestrant + alpelisib in 2nd line

CDK4/6i-naïve mBC: 11months mPFS (SOLAR-1[(a)])

CDK4/6i-pretreated mBC: 50.4% progression-free at 6 months, (BYLIEVE[(b)])

[(a)] Andre, NEJM 2019 ; [(b)] Rugo, Lancet Oncol 2021

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Limited efficacy of the 2nd line after progression on CDK4/6i

	mPFS		
elacestrant	3.8 months	*ESR1*$_{mut}$ mBC	100% CDK4/6i (+/- chemo) pre-treated, EMERALD trial [(a)]
fulvestrant + abemaciclib	6 months	All comers	100% CDK4/6i pre-treated, postMONARCH trial [(b)]
fulvestrant + capivasertib	7.3 months	PIK3CA/AKT/PTEN$_{mut}$ mBC	73% CDK4/6i pre-treated, CAPItello-291 trial [(c)]

[(a)] Bidard, JCO 2022 ; [(b)] Kalinsky, ASCO 2024 ; [(c)] Turner, NEJM 2023

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⇨ Extending the time on 1st line CDK4/6i is critical

Understanding acquired resistance mechanisms to CDK4/6i + AI

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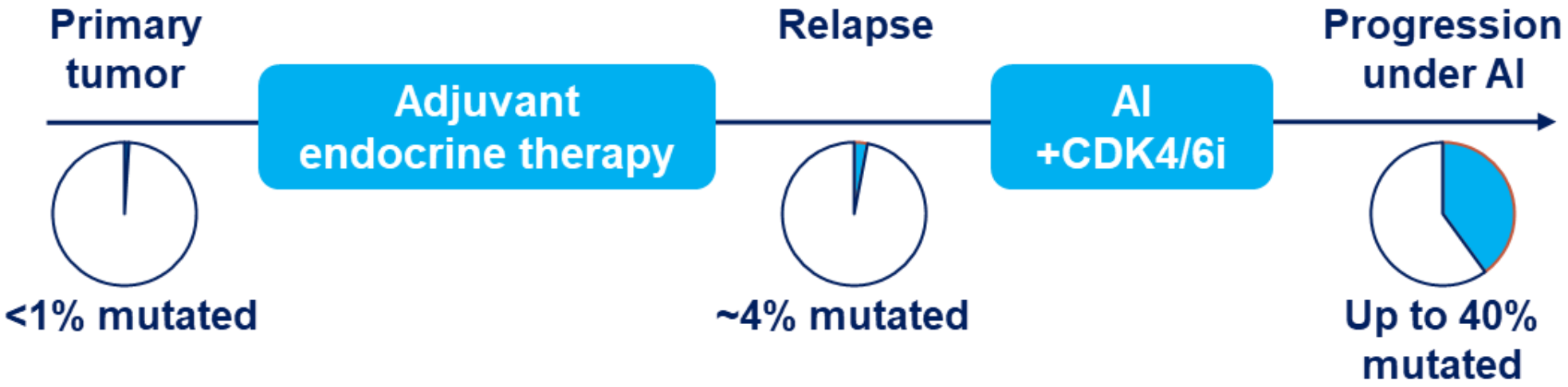
Understanding acquired resistance mechanisms to CDK4/6i + AI

CDK4/6i ➔ known resistance mechanisms are rare and not (yet) targetable

ESR1 mutations: a major opportunity… not to be missed !



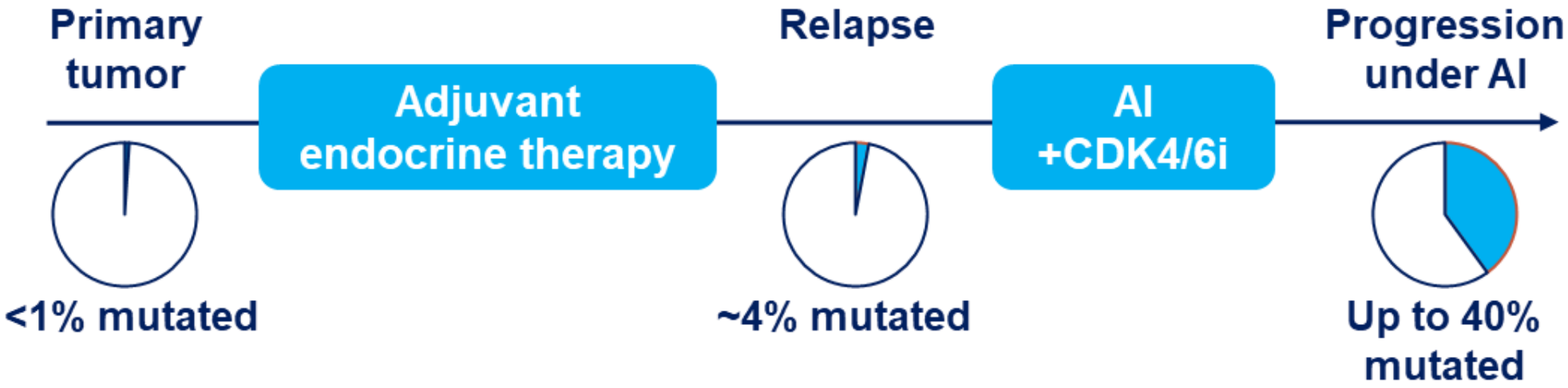
ESR1$_{mut}$ become detectable **during** AI + CDK4/6i

mutant clones rising in ctDNA

Tumor cells may still be sensitive to CDK4/6i

Figure adapted from Allouchery, BCR 2018; [a] Turner, CCR 2020; [b] Turner, Lancet Oncol 2020; [c] Bidard, JCO 2022

ESR1 mutations: a major opportunity… not to be missed !



$ESR1_{mut}$ become detectable **during** AI + CDK4/6i

Mutant estrogen receptors are degradable by **fulvestrant** (SoFEA & EFECT trials[a])

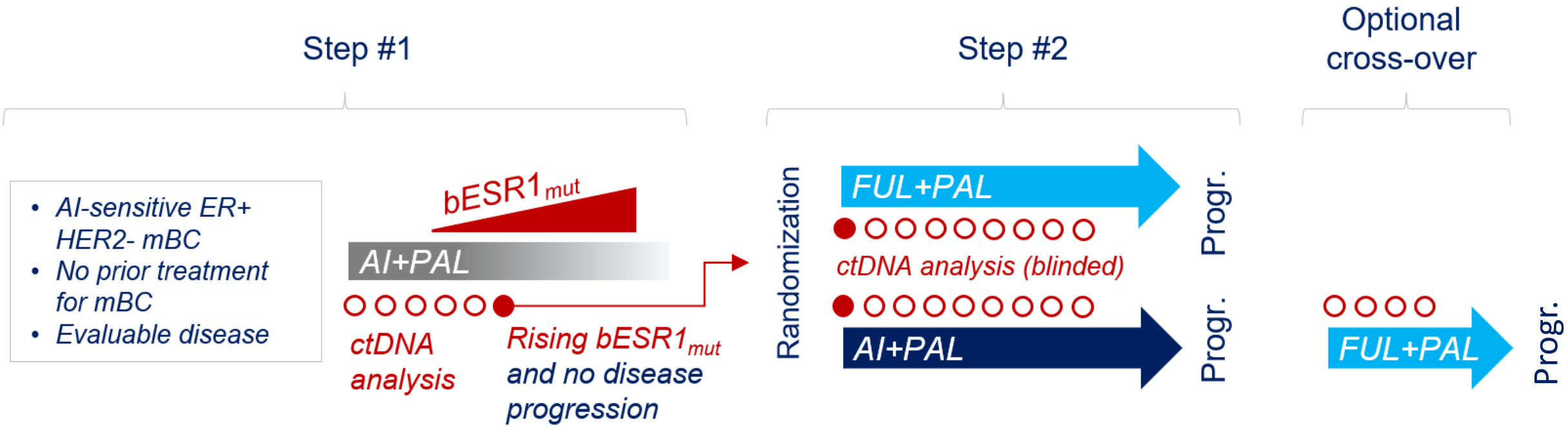
However, fulvestrant has **no relevant efficacy after disease progression**:

plasmaMATCH[b] **2.2 months** mPFS in $ESR1_{mut}$ mBC

EMERALD[c] **1.9 month** mPFS in $ESR1_{mut}$ mBC

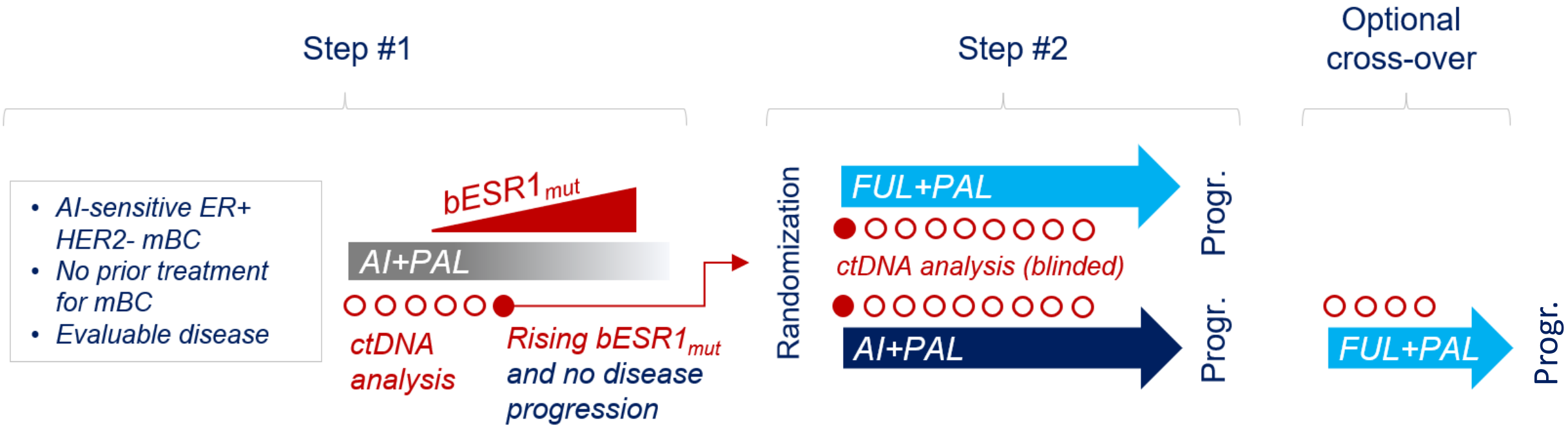
Figure adapted from Allouchery, BCR 2018; [a] Turner, CCR 2020; [b] Turner, Lancet Oncol 2020; [c] Bidard, JCO 2022

PADA-1, the academic proof-of-concept trial



PADA-1
THE RISE OF ESR1

PADA-1, the academic proof-of-concept trial



Delaying disease progression on CDK4/6i ?

Optimal use of SERD as a targeted therapy against $ESR1_{mut}$?

Feasibility / acceptance ?

Updated PFS results – primary endpoint

N= 1,017 pts enrolled in step #1

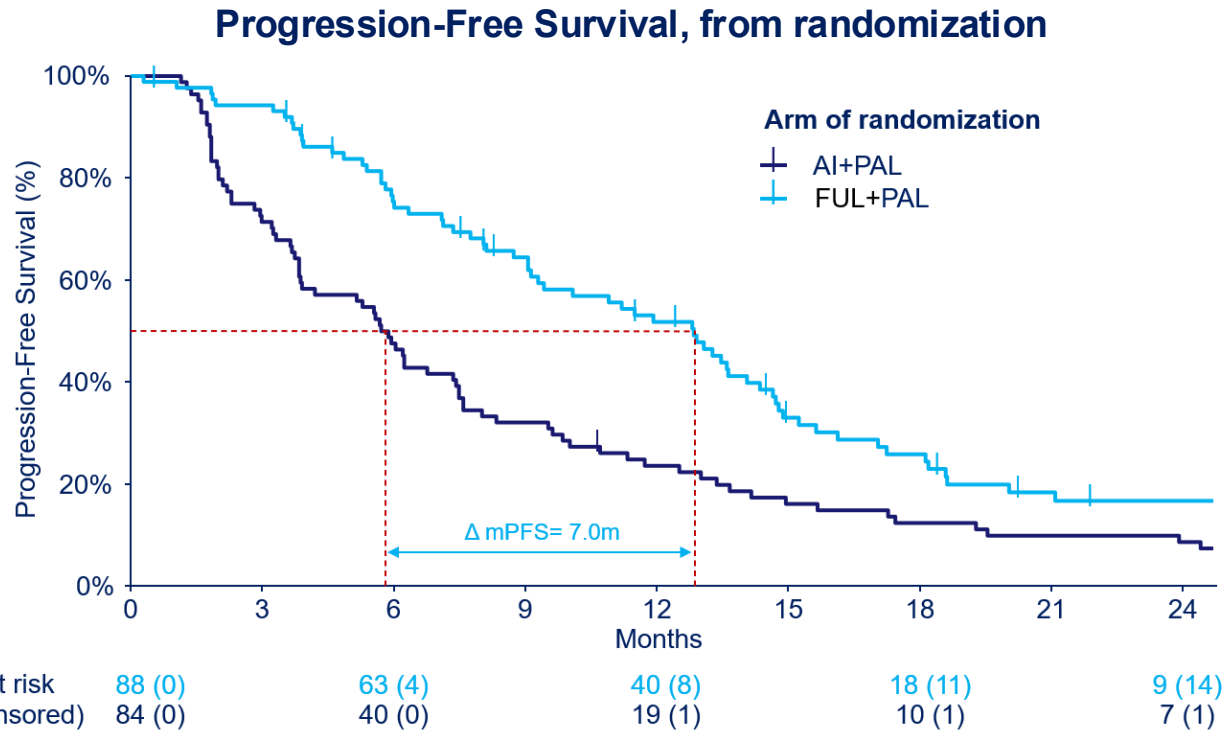
N= 283 pts with a rising *bESR1*$_{mut}$

while the study was ongoing

N= 172 pts randomized

- N= 88 pts allocated to FUL+PAL
- N= 84 pts allocated to AI+PAL

Data cut-off: June 21, 2022 Median FU from randomization: 28.2 months; N= 152 PFS events (89% maturity)



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]

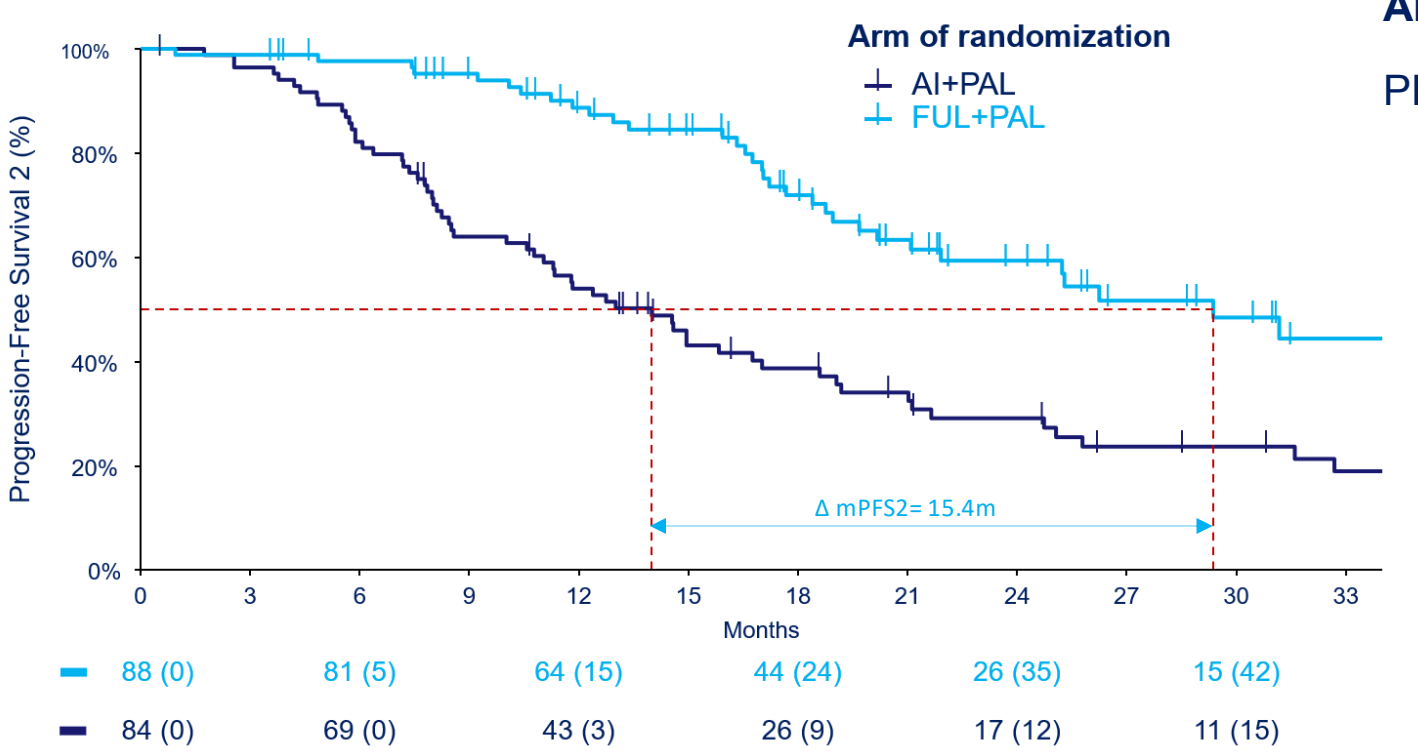
Optional cross-over (N=49 patients)
mPFS: 3.5 months, 95%CI [2.4;5.4]

Updated results presented at ASCO 2023; Primary results: Bidard, Lancet Oncol 2022

PFS2 results – secondary endpoint

Data cut-off: June 21, 2022 N= 93 PFS2 events (54% maturity)

Progression-Free Survival 2, from randomization



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

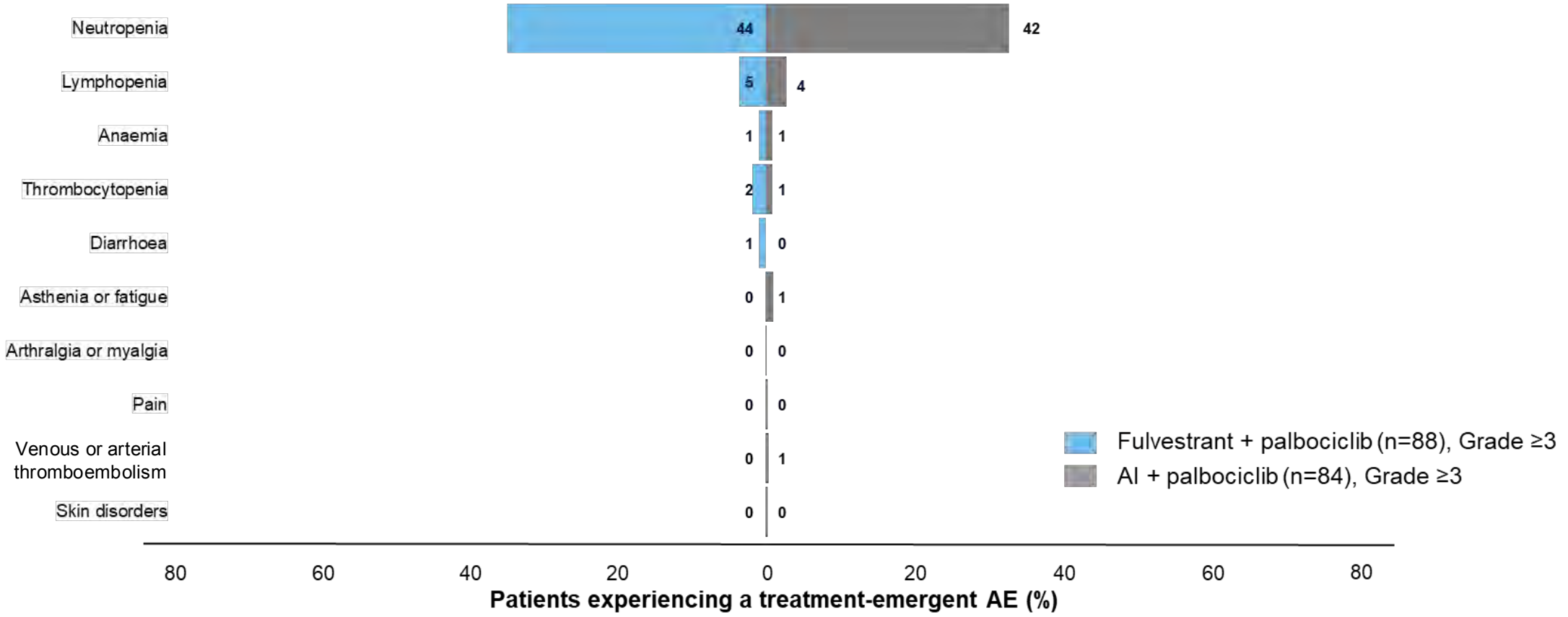
AI+PAL mPFS2: 14.0 months, 95%CI [11.0;18.6]

PFS2 HR= 0.37 [0.24;0.56]

PFS2: time from randomization to 2nd progression or death in both arms

Updated results presented at ASCO 2023; Primary results: Bidard, Lancet Oncol 2022

PADA-1 Safety– most frequent grade 3-4 AEs in step #2



Grade 3 and 4 AEs of interest are reported in the slide, only Grade ≥3 events are reported unless it was a serious AE.
AE=adverse event; AI=aromatase inhibitor.
Bidard FC, et al. *Lancet Oncol*. 2022;23:1367–1377.

Questions?

SERENA-6: the global trial with camizestrant (oral ngSERD)

- HR-positive, HER2-negative locally advanced (inoperable) or mBC[1,2]
- Currently receiving **AI** (anastrozole or letrozole) + **CDK4/6i** (palbociclib, abemaciclib or ribociclib) ± LHRH as 1L treatment for ≥6 months with no evidence of PD[1,2*]

Step 1: *ESR1*m detection

Continue 1L treatment with AI (anastrozole or letrozole) + CDK4/6i (**palbociclib, abemaciclib or ribociclib**) ± LHRH

***ESR1*m screening in plasma ctDNA** (every 2–3 treatment cycles) and **tumour imaging as per SoC**

***ESR1*m negative tumour** and no evidence of PD

***ESR1*m positive ctDNA** detected and no evidence of PD†

Step 2: Randomised treatment (N=300)[2]

R

1:1

Switch to camizestrant (75 mg QD) + maintain same CDK4/6i + placebo for AI

Continue on AI + maintain same CDK4/6i + placebo for camizestrant

SERENA-6 is the only Phase III study assessing an ngSERD in combination with all three approved CDK4/6i [1,2]

Primary endpoint[2]

- PFS*

Key secondary endpoints[2]

- PFS2, ORR, CBR_{24}, OS, PROs (TTD), time to ChT

*By investigator assessment; †Inclusion criteria for Step 2 include evaluable disease as per RECIST v1.1.[2]

1L=first-line; AI=aromatase inhibitor; CBR_{24}=clinical benefit rate at 24 weeks; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ChT=chemotherapy; CI=confidence interval; ctDNA=circulating tumour DNA; *ESR1*m=oestrogen receptor alpha mutation; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; LHRH=luteinising hormone-releasing hormone; mBC=metastatic breast cancer; ngSERD=next-generation selective oestrogen receptor degrader; ORR=objective response rate; OS=overall survival; PD=disease progression; PFS=progression-free survival; PRO=patient reported outcome; QD=once daily; R=randomisation; RECIST=response evaluation criteria in solid tumors; SoC=standard of care; TTD=time to deterioration.

1. NIH. SERENA-6. Available at: https://www.clinicaltrials.gov/study/NCT04964934 (Accessed September 2024); 2. Bidard F-C, et al. Presented at SABCS Annual Meeting 2021, December 7–10. San Antonio, Tx. Abstract #OT2-11-05.

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- PFS2, ORR, CBR_{24}, OS, PROs (TTD), time to ChT

Enrollment completed in 07/2024, read-out expected in 2025

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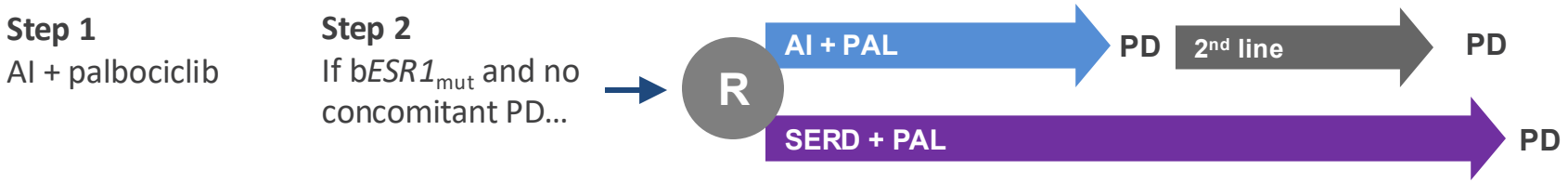
Potential benefits of intercepting *ESR1*$_{mut}$



Maximizing SERD efficacy: 6 mo absolute mPFS gain in PADA-1

vs ~2 mo mPFS if used after PD [7,8]

Targeting resistant subclones when they are still a minority ?

Results of a trial in *EGFR*$_{mut}$ NSCLC also support the concept of early targeting [9]

Extending the length of CDK4/6i exposure

Prof Bidard – Case Presentation

69 y.o. woman, retired seamstress

Family history: her sister had a breast cancer at age 50

Personal history: obesity (BMI=34), diabetes & hypertension

Diagnosed with de novo stage IV breast cancer, cT2N1 with many asymptomatic bone lesions, PS=0

Breast biopsy: ER+ 90%, PR+ 20%, HER2- (1+)

1st line treatment with letrozole and ribociclib has been initiated

Three months later, patient comes back to her planned consultation

- Treatment is very well tolerated
- CT scan shows stable bone lesions.
- Clinical exam shows a clinical response of the breast mass and axillary lymph nodes.

Prof Bidard – Case Presentation (Continued)

You also received the results of

- Somatic NGS testing (breast tumor tissue): *PIK3CA*$_{mut}$. No *ESR1*$_{mut}$ detected.
- Germline NGS testing (blood): no germline alteration.

Questions

- **Did you expect to find an *ESR1*$_{mut}$ in the tumor tissue ?**
- The likelihood to develop an *ESR1*$_{mut}$ during AI+CDK4/6i is ~40%

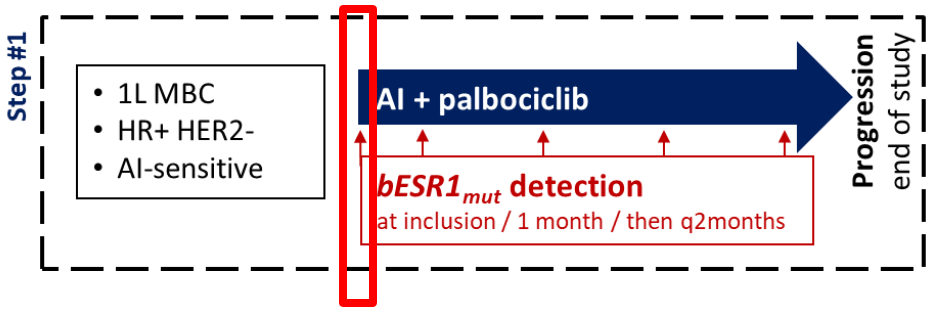
but **how do patients with either somatic *PIK3CA*$_{mut}$ or with *gBRCA2*$_{mut}$ behave in that regard ?**

Prof Bidard – Case Presentation (Continued)

- **Did you expect to find an *ESR1*$_{mut}$ in the tumor tissue ?**

No -- *ESR1*$_{mut}$ mostly appear **after** exposure to aromatase inhibitor, given for mBC

PADA-1



Prior to AI+PAL, N= 33 /1,017 pts **(3.2%)** were *ESR1*$_{mut}$-positive [4]

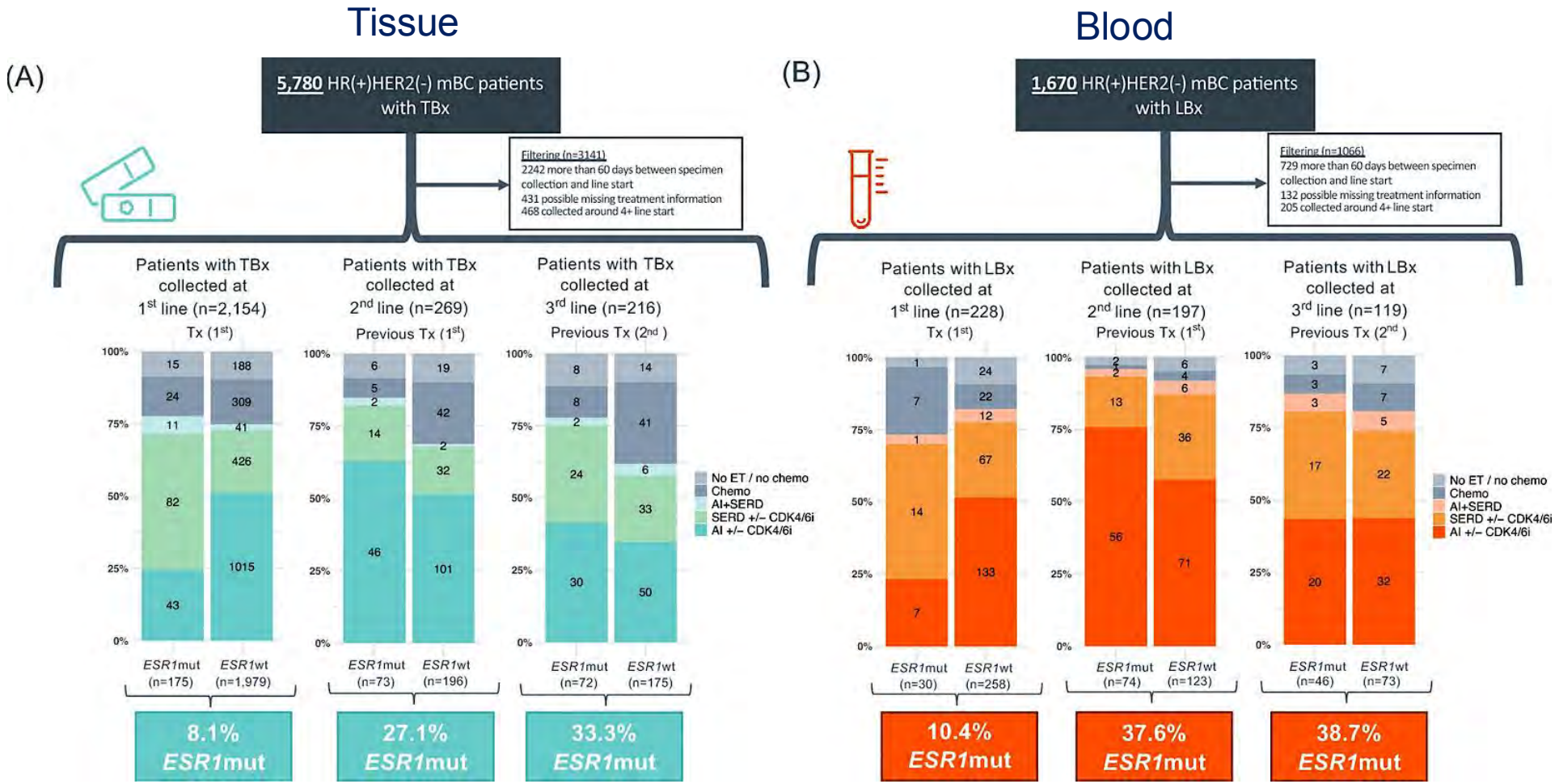
Factors associated with higher prevalence at mBC diagnosis

Bone mets:	detection rate:	**4.0%**; OR=3.4
Menopause:		**4.1%**; OR=5.4
Prior exposure to AI:		**7.1%**; OR=3.0

[4] Bidard *et al*, ASCO 2020, abstract 1010

Prof Bidard – Case Presentation (Continued)

Prevalence of *ESR1*$_{mut}$ in samples analyzed by CDx 2011-2023



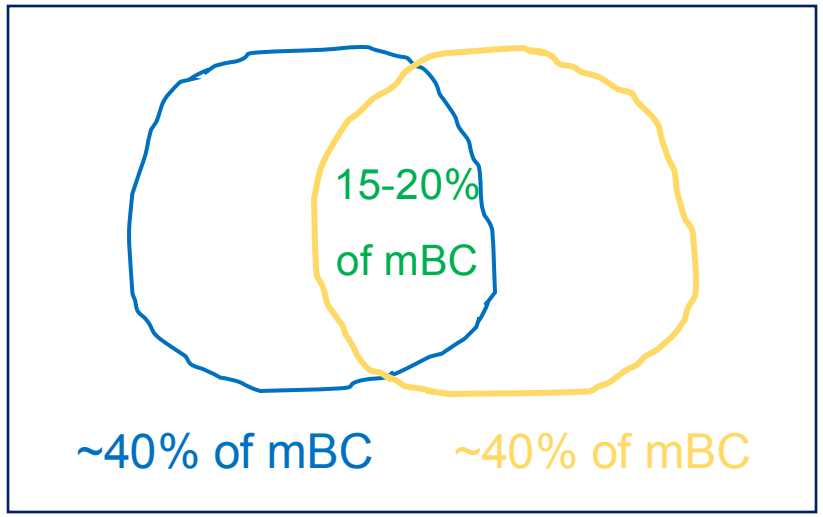
Bhave, BCRT 2024

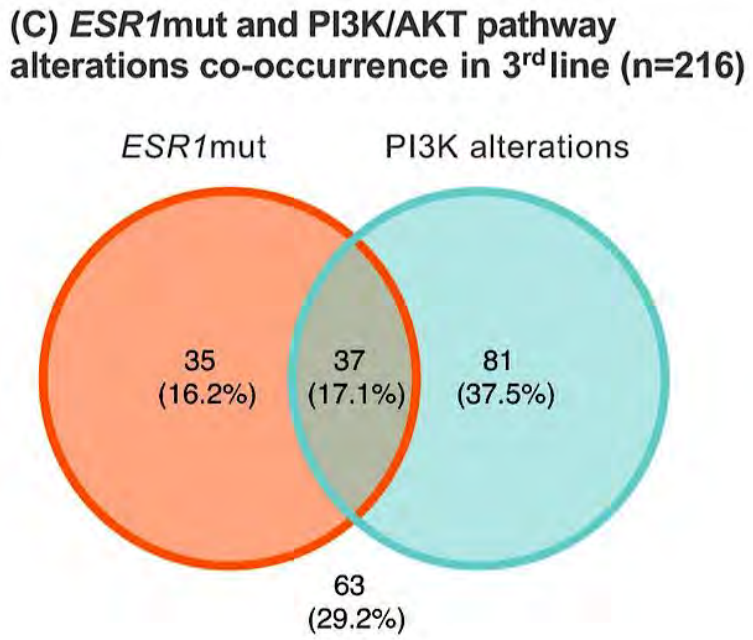
Prof Bidard – Case Presentation (Continued)

- Does the presence of *PIK3CA*$_{mut}$ or *gBRCA2*$_{mut}$ influence the appearance of *ESR1*$_{mut}$?

No *PIK3CA*$_{mut}$ are detected in ~40% of BC

ESR1$_{mut}$ incidence is independent of *PIK3CA*$_{mut}$ status





Bhave, BCRT 2024

Prof Bidard – Case Presentation (Continued)

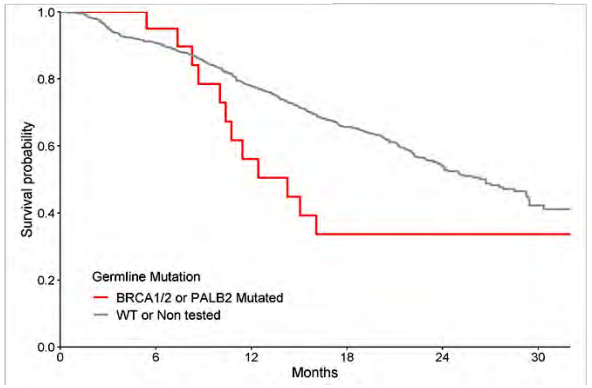
- Does the presence of *PIK3CA$_{mut}$* or *gBRCA2$_{mut}$* influence the appearance of *ESR1$_{mut}$* ?

No

gBRCA2$_{mut}$

- shortened PFS on AI+CDK4/6, due to a frequent co-loss of BRCA2 and RB1 in tumors (a)
- PADA-1: no impact on the onset of *ESR1$_{mut}$* (b)

Median PFS according to gBRCA1/2/PALB2 status

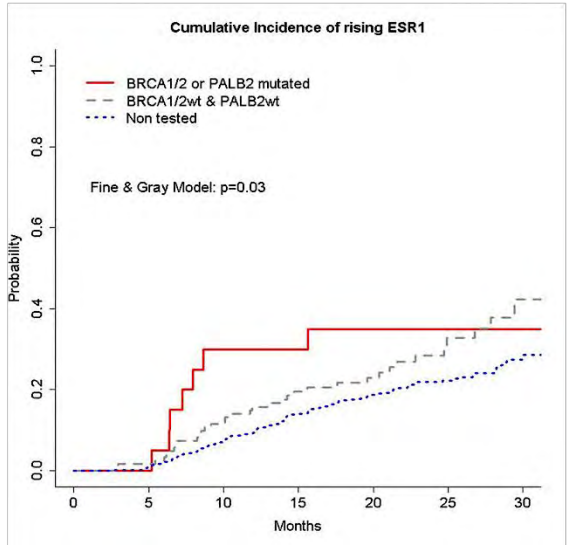


Incidence of rising ESR1 mutation

gBRCA1/2/PALB2 mutated: n=7/20 (35%)
(Median follow-up: 22.2m IC95% [16.3 ; NR])

gBRCA1/2/PALB2 non mutated: n=35/125 (28%)
(Median follow-up: 20.6m IC95% [19.4 ; 22.3]

gBRCA1/2/PALB2 non tested: n=176/872 (20%)
(Median follow-up 21.2m IC95% [20.7; 21.6])



[4] Safonov, bioRxiv 2024; (b) Fresnel, ESMO 2020

Prof Bidard – Case Presentation (Continued)

You are telling the patient about the risk of $ESR1_{mut}$ appearing during therapy.

What are the main talking points ?

She understands the benefits and is willing to begin non-invasive monitoring by serial ctDNA analyses.

… but **when do you test, and at which frequency ?**

Prof Bidard – Case Presentation (Continued)

Main talking points (suggestion)

- Her mBC is very likely to develop a resistance to either therapy of the combination she is receiving
- If the disease progresses, subsequent treatment lines may be more toxic and with limited efficacy
- Part of her routine monitoring of the tumor response to therapy, serial blood draw can detect some form of tumor resistance in ~40% of patients.
- It is possible to switch to the endocrine therapy if a resistance to the first endocrine therapy is detected, while continuing CDK4/6 inhibition, thus delaying the time of tumor progression

+ discuss the timing of blood analyses… when their results will be known (and if the patient should expect a call)

Prof Bidard – Case Presentation (Continued)

When do you test ? At which frequency ? (suggestions)

- **<u>Not</u> before 6 months on AI+CDK4/6i**

  few *ESR1*$_{mut}$ detected before 6 months

  mBC resistance within the first 6 months = endocrine-refractory; an ET switch unlikely to have any impact

[a] Berger, BMJ Open 2022; [b] Turner, Future Oncol 2023

Prof Bidard – Case Presentation (Continued)

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- **At anytime thereafter**

  ESR1$_{mut}$ screening can be initiated in any patient under AI+CDK4/6i, as long the disease has not yet progressed

  Note that the first ctDNA analysis has a higher probability to be positive than the following (pts should be warned)

Prof Bidard – Case Presentation (Continued)

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  Note that the first ctDNA analysis has a higher probability to be positive than the following (pts should be warned)

- **Frequency ?**

  every 2 months in PADA-1 [(b)]

  every 3 months in SERENA-6 [(c)]

  Other, non-evidence based: longer interval ?

  tumor growth not reaching RECIST PD criteria ? Or other early sign of resistance ?

[(a)] Berger, BMJ Open 2022; [(b)] Turner, Future Oncol 2023

Prof Bidard – Case Presentation: Same Patient, 2 Years Later

After 2 years on letrozole+ribociclib, ctDNA analysis reports an *ESR1*$_{mut}$.

The ctDNA report shows the *ESR1*$_{mut}$ has been detected at a very low allelic fraction (0.5%), while *PIK3CA*$_{mut}$ was found at 1.3%.

What is/are the best thing(s) to do ?

- Wait until the next blood draw to confirm *ESR1*$_{mut}$ positivity
- Request a tumor evaluation
- Discuss with patient an immediate switch from letrozole+ribociclib to SERD+ribociclib

Prof Bidard – Case Presentation: Same Patient, 2 Years Later (Continued)

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What is/are the best thing(s) to do ?

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No need of a confirmation…

- False positive results are exceptional with current ctDNA analyses
- Subclonality is frequent for *ESR1*$_{mut}$

Prof Bidard – Case Presentation: Same Patient, 2 Years Later (Continued)

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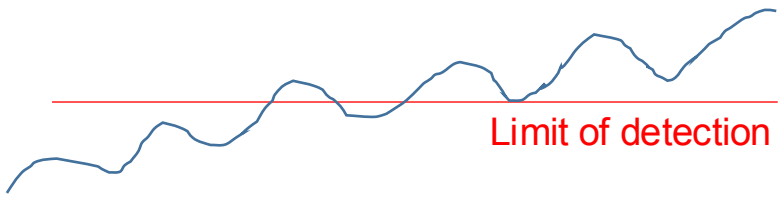

No need of a confirmation…

- False positive results are exceptional with current ctDNA analyses
- Subclonality is frequent for *ESR1*$_{mut}$

Rising *ESR1*$_{mut}$ detection made at the limit of detection (~0.1-0.5%)

- Low allelic fraction is typical of the first detection of a rising ctDNA

PADA-1: median MAF = 0.8% [(a)]

- *ESR1*$_{mut}$ may be missed in a second sample

PADA-1: *ESR1mut* not detected in ~40% of pts at next blood draw [(a)]

[(a)] Bidard, ASCO 2023

Prof Bidard – Case Presentation: Same Patient, 2 Years Later (Continued)

After 2 years on letrozole+ribociclib, ctDNA analysis reports an *ESR1*$_{mut}$.

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What is/are the best thing(s) to do ?

- ~~Wait until the next blood draw~~

The next blood draw may be too late !

ctDNA in PADA-1 was detected by ddPCR:

~25% of patients with rising *ESR1*$_{mut}$ had a synchronous progression

ctDNA in SERENA-6: NGS

Factors influencing the rate of patients with synchronous progression:

- ctDNA test sensitivity
- Interval between two tests
- Biologic features

Prof Bidard – Case Presentation: Same Patient, 2 Years Later (Continued)

After 2 years on letrozole+ribociclib, ctDNA analysis reports an *ESR1*$_{mut}$.

The ctDNA report shows the *ESR1*$_{mut}$ has been detected at a very low allelic fraction (0.5%), while *PIK3CA*$_{mut}$ was found at 1.3%.

What is/are the best thing(s) to do ?

- Request a tumor evaluation
- Discuss with patient an immediate switch from letrozole+ribociclib to SERD+ribociclib

Benefit to extend the 1st line & limited toxicity ➔ attractive option

Not in current clinical guidelines -- as of October 2024

- At the moment, relies only on PADA-1 results. SERENA-6 trial will read out in 2025
- Only SERD available now: Fulvestrant (IM shots, etc).
- Camizestrant may become the only ngSERD with a label for the switch, depending on SERENA-6 results

Prof Bidard – Case Presentation: Same Patient, 2 Years Later (Continued)

Patient has no synchronous disease progression and *ESR1*$_{mut}$ in ctDNA triggered a switch to a SERD+ribociclib

How do you monitor the disease after the switch ? (ctDNA, imaging…)

Prof Bidard – Case Presentation: Same Patient, 2 Years Later (Continued)

Patient has no synchronous disease progression and *ESR1*$_{mut}$ in ctDNA triggered a switch to a SERD+ribociclib

How do you monitor the disease after the switch ? (ctDNA, imaging…)

There is NO data to support the utility *ESR1*$_{mut}$ monitoring during SERD-based therapy

Clearance/decrease of ctDNA ➔longer PFS in several reports…

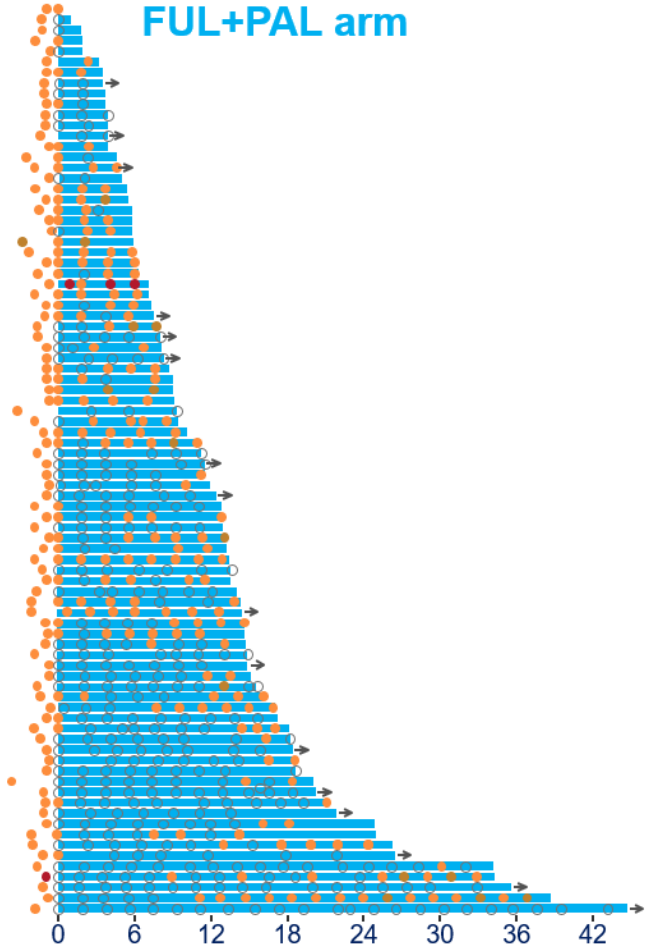
… but no threshold a timing validated / no benefit demonstrated

Rising ctDNA is an easy call (from negative to positive results)

and is clinically actionable

But, once switched, patients should rather discontinue ctDNA monitoring

(unless within a research program)



Bidard, ASCO 2023

Agenda

Introduction: Confronting Metastatic Breast Cancer (mBC)

Module 1: Mechanisms of Resistance to Endocrine Therapy in HR-Positive mBC; Use of Oral Selective Estrogen Receptor Degraders (SERDs) — Dr Kalinsky

Module 2: Ongoing Evaluation of Early Therapeutic Switching for HR-Positive mBC Harboring ESR1 Mutations — Prof Bidard

Module 3: Other Key Datasets and Ongoing Trials in HR-Positive Breast Cancer

Key Datasets and Ongoing Trials: Adjuvant Therapy

Ignatiadis M et al. EORTC-2129-BCG: **Elacestrant** for treating ER+/HER2- breast cancer patients with **ctDNA relapse (TREAT ctDNA)**. ESMO 2024;Abstract 338TiP.

Hamilton E et al. A phase III randomised open-label study of **extended adjuvant therapy with camizestrant vs standard endocrine therapy (ET)** in patients with ER+/HER2– early breast cancer (BC) and an intermediate or high risk of recurrence (**CAMBRIA-1**) ESMO 2023;Abstract 354 TiP.

NCT05952557. An **adjuvant endocrine-based therapy study of camizestrant** (AZD9833) in ER+/HER2- early breast cancer (CAMBRIA-2).

Jhaveri K et al. **EMBER-4: A phase 3 adjuvant trial of imlunestrant vs standard endocrine therapy (ET)** in patients with ER+, HER2- early breast cancer (EBC) with an increased risk of recurrence who have previously received 2 to 5 years of adjuvant ET. SABCS 2022;Abstract OT1-01-02.

Geyer C et al. **lidERA** Breast Cancer (BC): **Phase III adjuvant study of giredestrant vs physician's choice of endocrine therapy** (PCET) in patients (pts) with estrogen receptor-positive, HER2-negative early BC (ER+, HER2– eBC). ASCO 2023;Abstract TPS616.

Key Datasets and Ongoing Trials: Neoadjuvant Therapy or Window of Opportunity

Vidal M et al. Solti-1905. **Elacestrant in preoperative setting**, a window of opportunity study (**ELIPSE** trial). SABCS 2022;Abstract PD13-01.

Robertson J et al. **SERENA-3: A randomized pre-surgical window of opportunity study** assessing dose and duration of **camizestrant** treatment in postmenopausal women with ER-positive, HER2-negative primary breast cancer. SABCS 2023;Abstract RF01-01.

Neven P et al. A **preoperative window-of-opportunity** (WOO) study of **imlunestrant** in ER+, HER2- early breast cancer (EBC): Final analysis from **EMBER-2**. ESMO 2023;Abstract 273P.

Hurvitz SA et al. **Neoadjuvant palbociclib plus either giredestrant or anastrozole** in oestrogen receptor-positive, HER2-negative, early breast cancer (**coopERA** Breast Cancer): An open-label, randomised, controlled, phase 2 study. *Lancet Oncol* 2023;24(9):1029-41.

Key Datasets and Ongoing Trials: Proteolysis Targeting Chimeras (PROTACS)

Hamilton E et al. First-in-human safety and activity of **ARV-471**, a novel **PROTAC estrogen receptor degrader**, in ER+/HER2- locally advanced or metastatic breast cancer. SABCS 2021;Abstract PD13-08.

Hamilton E et al. **Vepdegestrant**, a proteolysis targeting chimera (PROTAC) estrogen receptor (ER) degrader, **plus palbociclib** (palbo) in ER+/human epidermal growth factor receptor 2 (HER2)- advanced breast cancer: Updated **phase Ib cohort** results. ESMO Breast 2024;Abstract 218P.

Hamilton E et al. **VERITAC-2**: A global, randomized **phase 3 study of ARV-471**, a PROteolysis TArgeting Chimera (PROTAC) estrogen receptor (ER) degrader, **vs fulvestrant** in ER+/human epidermal growth factor receptor 2 (HER2)- advanced breast cancer. ESMO Breast 2023;Abstract 257TiP.

Wander S et al. **VERITAC-3**: A randomized **phase 3 study**, with a lead-in, of **first-line vepdegestrant + palbociclib vs letrozole + palbociclib** in estrogen receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer. SABCS 2023;Abstract PO2-20-03.

Hamilton E et al. **AC699**, a novel chimeric estrogen receptor degrader, in a **phase I study** in breast cancer. ESMO 2024;Abstract 637P.

Case 2: First-Line Treatment of HR-Positive/HER2-Negative *PIK3CA*-Mutated Metastatic Breast Cancer

Dr Kalinsky – Case Presentation

- Patient is a 65-yo **postmenopausal** healthy female who is diagnosed with a right breast invasive ductal carcinoma, grade 2, ER+ 100% PR+ 100% HER2 0
- She undergoes lumpectomy, SLNB: 3 cm, 2/3 lymph nodes in 4/21
- Oncotype 20
- No chemo. s/p XRT
- Compliant with aromatase inhibitor. s/p 1 year of Abemaciclib – stopped in 6/22 due to intolerance
- Develops new bone metastases in 5/24 while on an aromatase inhibitor
- Her performance status is excellent
- She has **minimal pain** from metastases
- Hereditary Genetic Testing: no pathogenic variants

Dr Kalinsky – Case Presentation (Continued)

- She undergoes ctDNA testing: biomarker testing reveals a pathogenic *PIK3CA* H1047R mutation

What therapy would you recommend next?

1. Alpelisib + fulvestrant
2. Chemotherapy
3. Capivasertib + fulvestrant
4. Ribociclib + fulvestrant
5. Trastuzumab Deruxtecan
6. Sacituzumab Govitecan

Dr Kalinsky – Case Presentation (Continued)

- Pt started fulvestrant + ribociclib

The Implications of Recent Datasets for the Current and Future Management of Gastrointestinal Cancers — An ESMO Congress 2024 Review

A CME/MOC-Accredited Live Webinar

Tuesday, October 15, 2024
5:00 PM – 6:00 PM ET

Faculty

Tanios Bekaii-Saab, MD
Philip A Philip, MD, PhD, FRCP

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

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