Applying New Endocrine and Targeted Agents to the Treatment of Hormone Receptor Positive, HER2 Negative Breast Cancer

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Introduction

- For decades, endocrine therapy targeting estrogen receptor signaling has been a cornerstone in the treatment of breast cancer patients with estrogen receptor expression.
- However, the emergence of drug resistance remains a major clinical challenge. Therefore, the development of novel therapeutic agents capable of effectively inhibiting ERα activity is essential.
- The landscape of metastatic breast cancer treatment is rapidly evolving, not only with advancements in endocrine therapy but also through the integration of next-generation sequencing (NGS).
- NGS helps identify key genetic drivers, facilitating the development of targeted therapies. Ongoing research focuses on optimizing the combination and sequencing of these treatments to enhance patient outcomes.

First line Treatment for Metastatic HR+ BC ET+ CDK4/6 Offers Survival Advantage

	Situation	OS observed	HR
Monaleesa 2 (Hortobagyi NEJM 2022)	Endocrine-sensitive: Letrozole Letrozole + ribociclib	51.4 months 63.9 months	0.76 (0.63-0.93)
Paloma 2 (Finn ASCO 2022)	Endocrine-sensitive: Letrozole Letrozole + palbociclib	51.2 months 53.9 months	0.95 (0.77-1.17)
Monarch 3 (ESMO 2022)(**INTERIM**)	Endocrine-sensitive: NSAI NSAI + abemaciclib	54.5 months 67.1 months	0.84 (0.63-1.05)
Paloma 3 (Turner NEJM 2018, ASCO 2021)	Endocrine-resistant : Fulvestrant Fulvestrant + palbociclib	28.0 months (23.6-34.6) 34.9 months (28.8-40)	0.80 (0.65-0.99)
Monaleesa 3 (last Neven 2023 exploratory)	Endocrine-mixed : Fulvestrant Fulvestrant + ribociclib	51.8 months (40.4-61.2) 67.6 months (59.6 - NA)	0.67 (0.50-0.90)
Monarch 2 (Sledge JAMA oncol 2020)	Endocrine-mixed : Fulvestrant Fulvestrant + abemaciclib	37.3 months 46.7 months	0.78 (0.61-0.95)
Monaleesa 7 (Im NEJM 2019, Lu CCR 2022)	Endocrine-mixed : Letrozole Letrozole + ribociclib	48 months 58.7 months	0.76 (0.61-0.96)

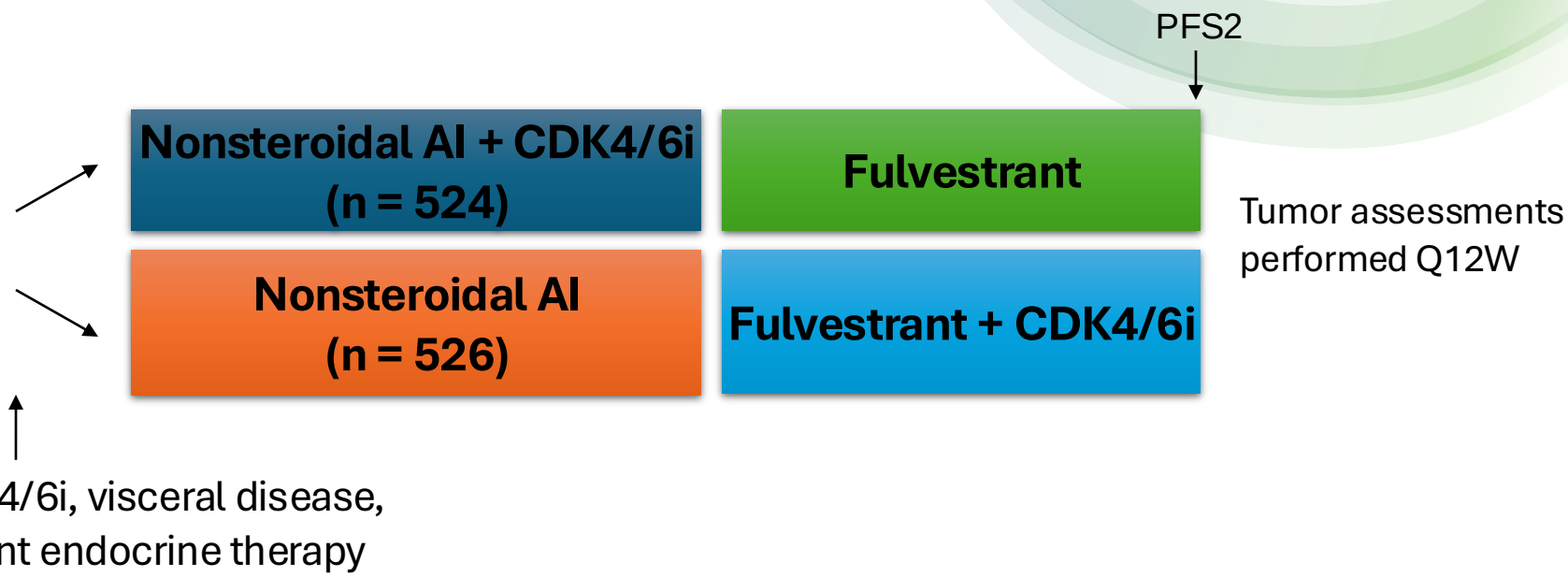
Hortobagyi GN NEJM 2016
Hortobagyi GN NEJM 2022
Tripathy D Lancet Oncol 2018
Lu YS Clin Cancer Res 2022
Johnston *NPJ Breast Cancer*. 2019
Johnston S, SABCS 2023
Finn RS NEJM 2016
Finn RS JCO 2022

Should ALL patient be started on CDK4/6i?

SONIA Trial: Study Design

- Patients with HR+/HER2- MBC
- No prior tx in MBC setting
- Neoadjuvant Tx allowed if DFS >12 mo after nonsteroidal AI
- No visceral crisis

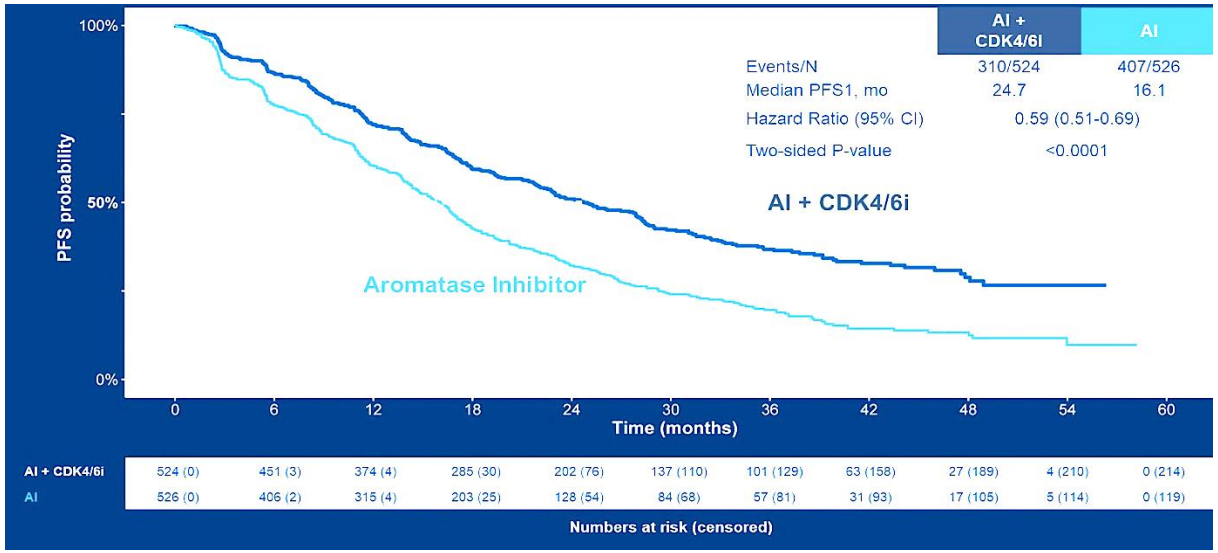
(N = 1050)

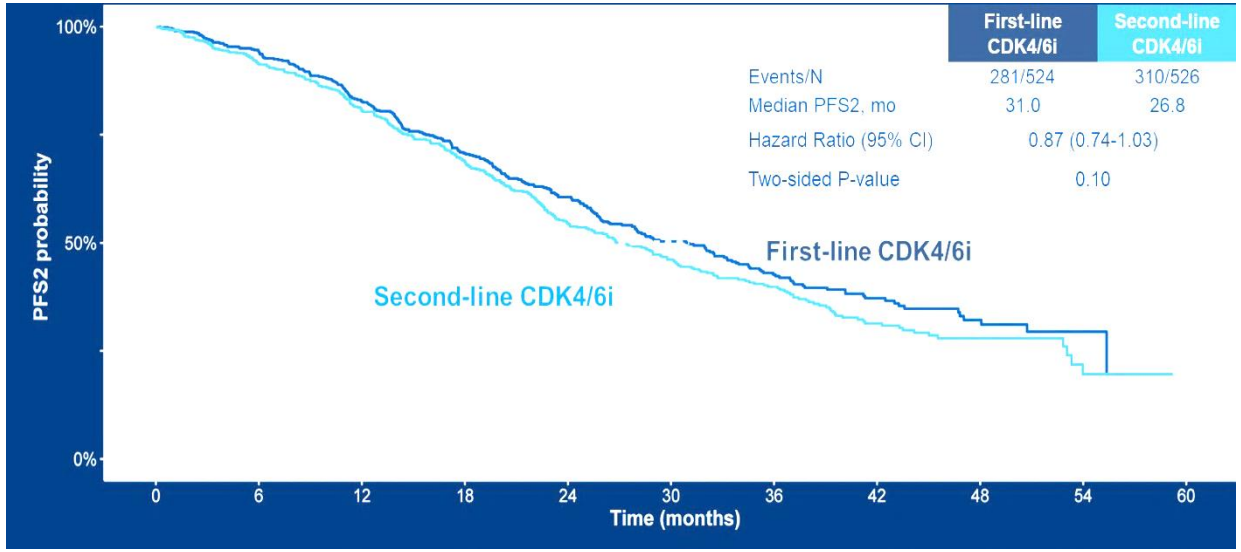


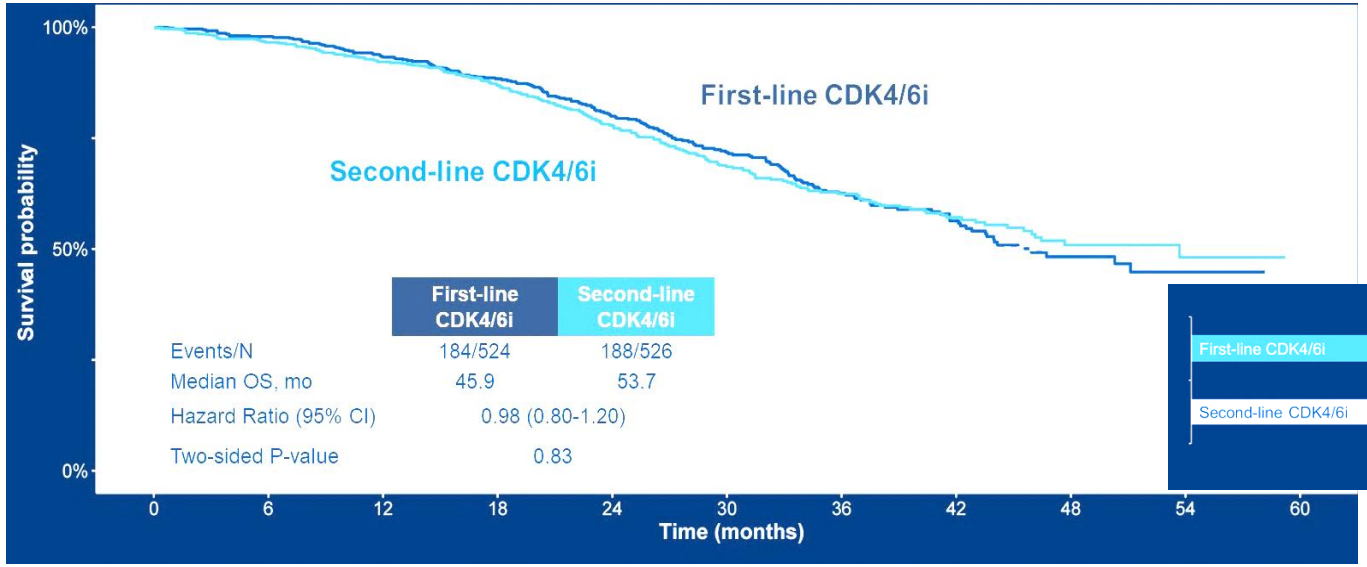
Primary endpoint: PFS2 (time from randomization to second disease progression or death)

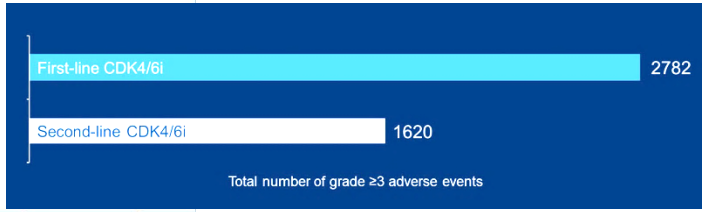
Sonke. ASCO 2023. Abstr LBA1000.

Sonia Trial Results: PFS1, PFS2, and OS







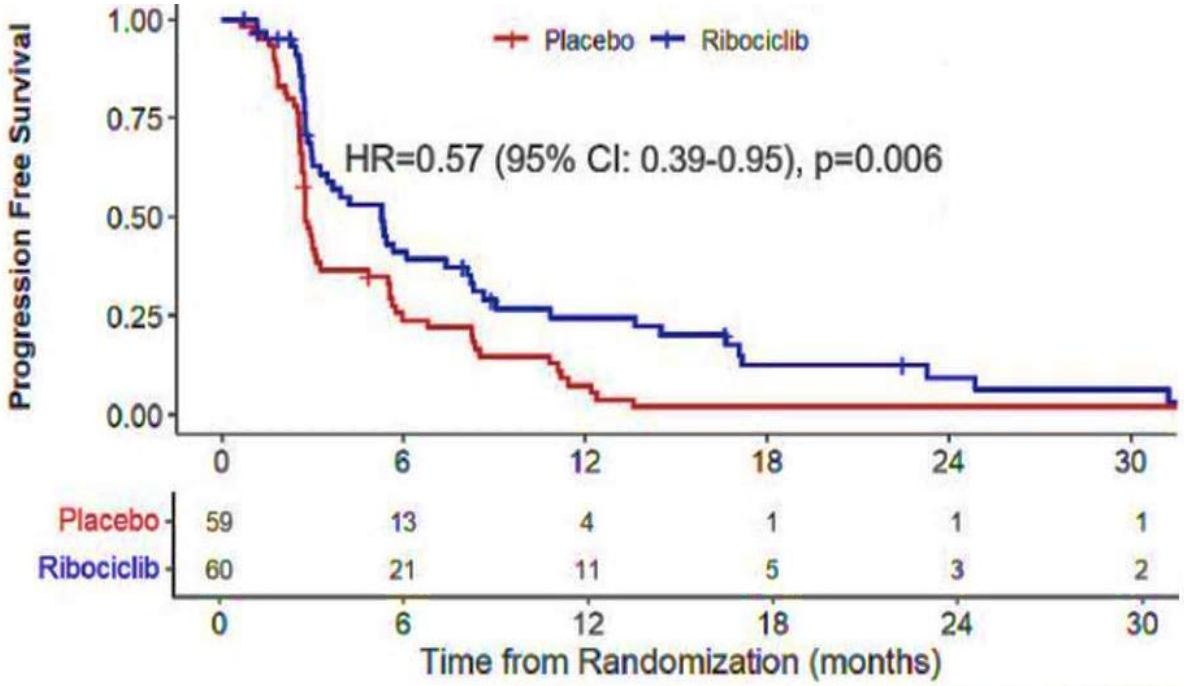


Sonke. ASCO 2023 LBA1000

The Switch Game Upon Progression…

MAINTAIN TRIAL PFS

ET +/- Ribociclib after Palbociclib



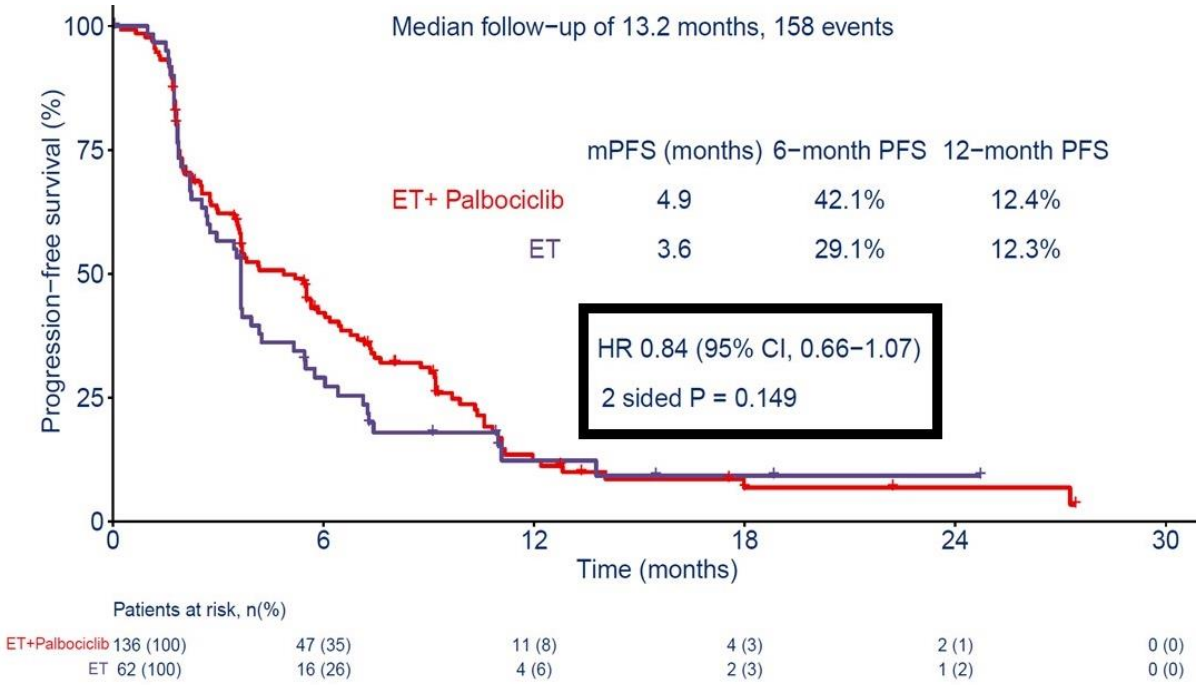
Kalinsky *JCO* 2023

Significant benefit of CDK4/6i switch Palbo→Ribo

The Switch Game Upon Progression…

PALMIRA TRIAL PFS

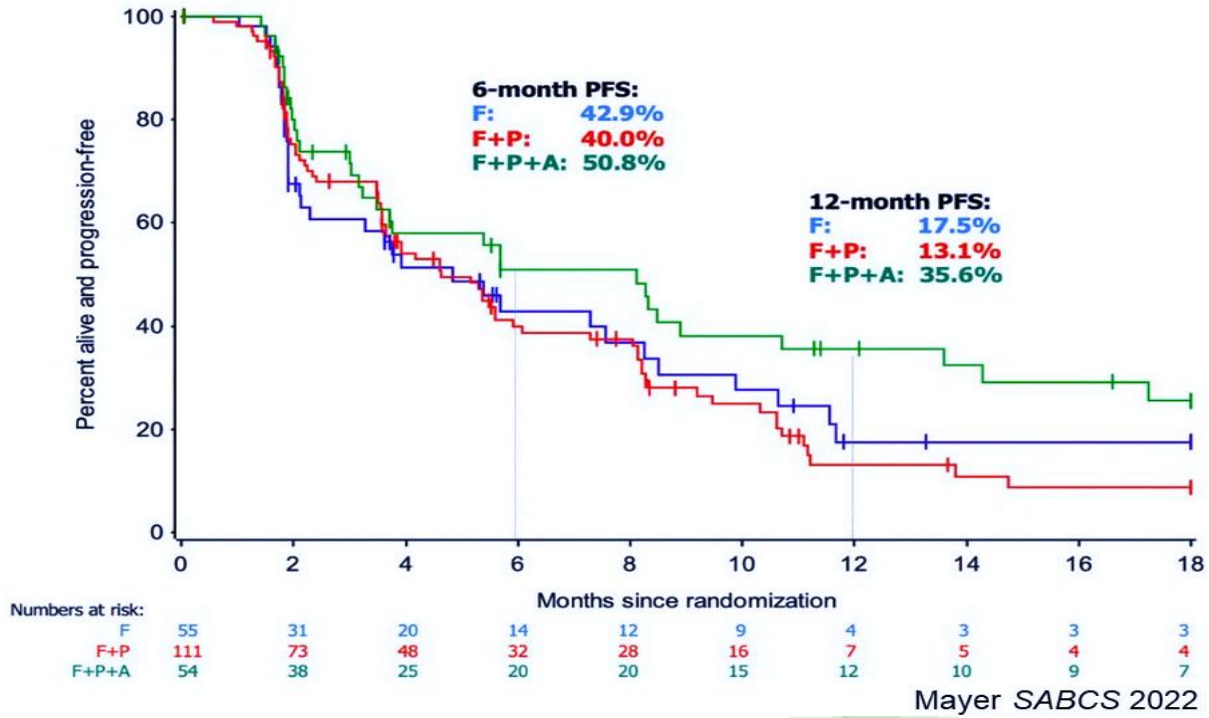
ET +/- Palbociclib after Palbociclib



Llombart-Cussac ASCO 2023

PACE TRIAL PFS

Fulvestrant +/- Palbociclib after Palbociclib



Mayer *SABCS 2022*

No PFS benefit in ET switch and keeping same CDK4/6i

Palbo→Palbo

The Switch Game Upon Progression…

postMONARCH Study Design

Eligibility

HR+, HER2- ABC

Men & Pre/post menopausal women

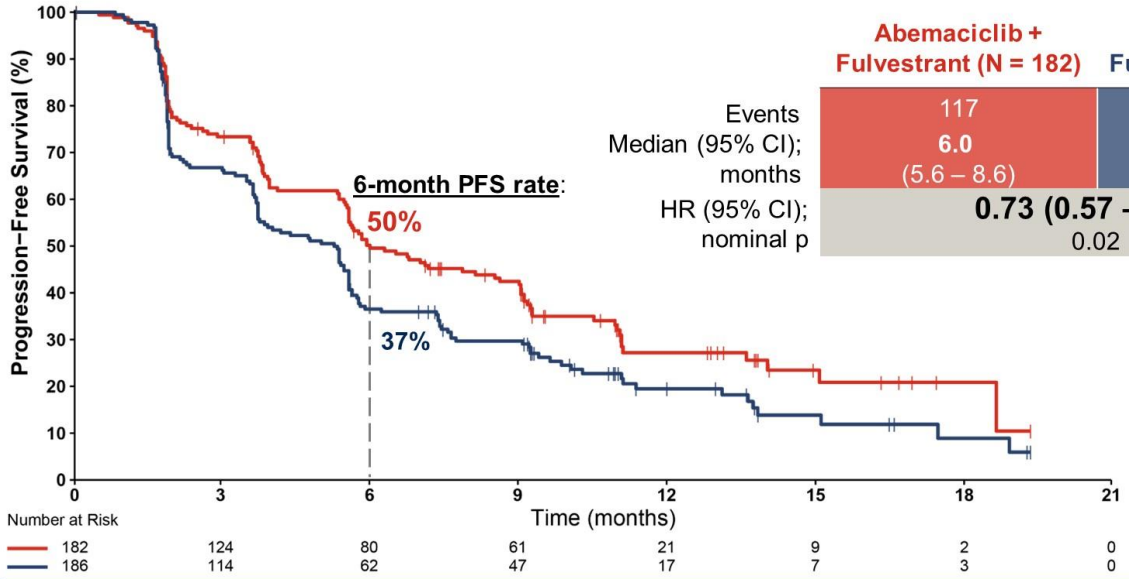
Prior Therapy:
- **ABC**: Disease progression on CDK4/6i + AI as initial therapy
- **Adjuvant**: Disease recurrence on/after CDK4/6i + ET
- No other therapy for ABC

Randomization 1:1

N = 368

- Abemaciclib + Fulvestrant
- Placebo + Fulvestrant

Primary Analysis: Abemaciclib Improved Investigator-Assessed PFS

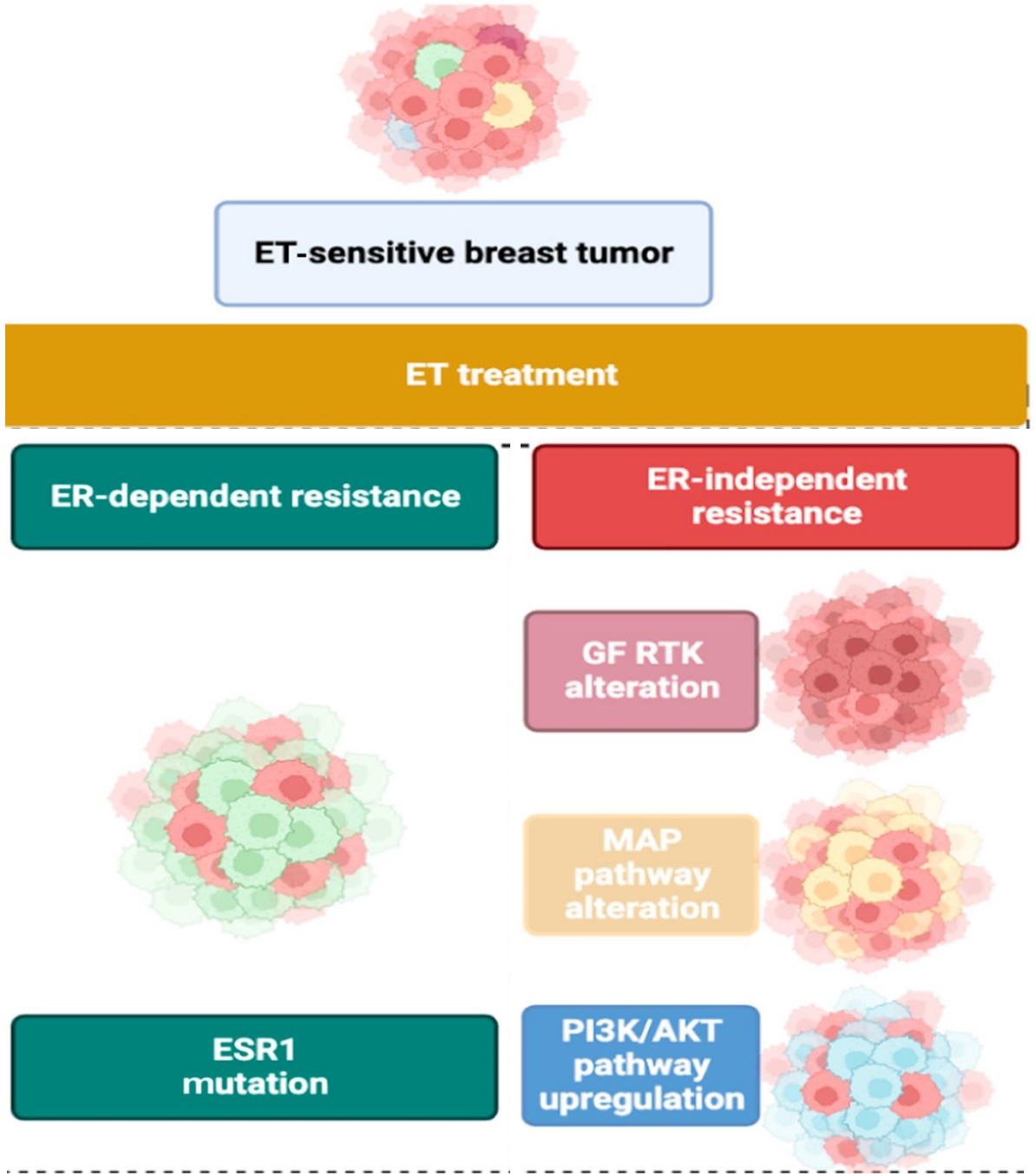


	Abemaciclib + Fulvestrant (N = 182)	Placebo + Fulvestrant (N = 186)
Events	117	141
Median (95% CI); months	6.0 (5.6 – 8.6)	5.3 (3.7 – 5.6)
HR (95% CI); nominal p	0.73 (0.57 – 0.95) 0.02	

Abemaciclib led to 27% reduction in the risk of developing PFS event

PRESENTED BY: Kevin Kalinsky, MD, MS

ET Resistance Mechanisms



Gnant M, et al Am Soc Clin Oncol Educ Book 2023

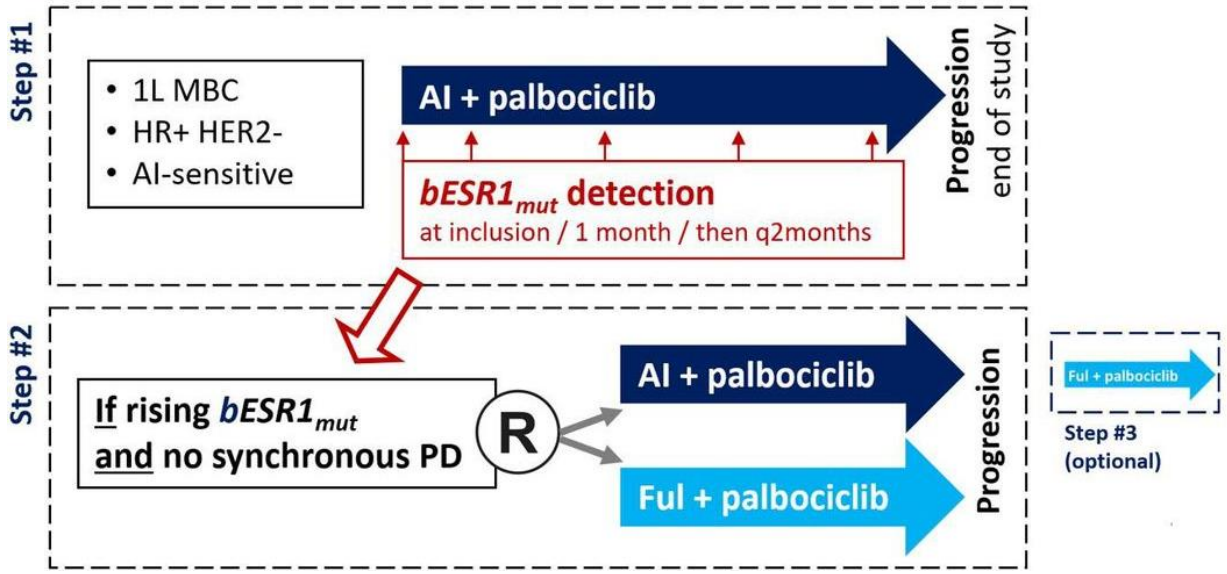
Table 1. Frequency of *ESR1*m after AI (mono or combination therapy).

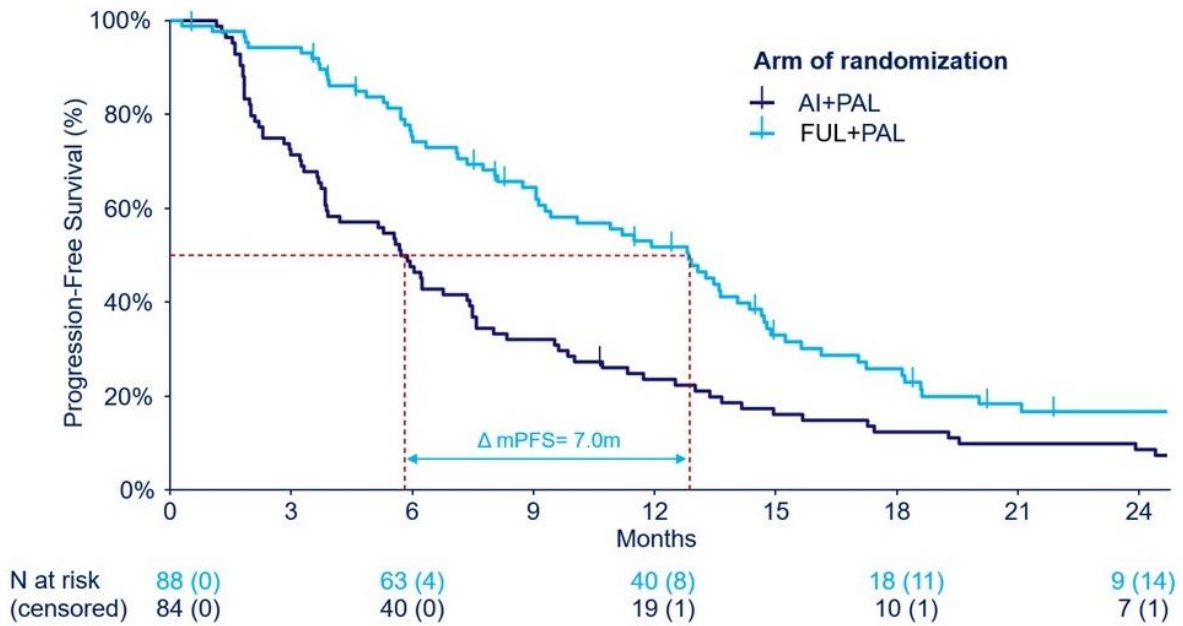
Trial	Tumor characteristics	Timing of test	Test (sample)	*ESR1*m frequency	N, *ESR1*m/total
MONARCH 3	Endocrine-therapy-naive HR+/HER2- ABC treated with 1L AI monotherapy (control arm)	End of 1L AI treatment	NGS (plasma)	31%	NR
EMERALD	One or two previous lines of endocrine therapy, at least one in combination with CDK4/6i	Start of 2L or 3L treatment	NGS (plasma)	48%	228/477
GuardantINFORM database	At least one previous AI therapy	Post-AI therapy	NGS (plasma)	31%	2044/6541
SoFEA/EFECT	HR+ mBC that had progressed on previous AI monotherapy	Start of 2L treatment	ddPCR (plasma)	30%	151/383
BOLERO-2	HR+ ABC that had progressed on previous AI monotherapy	Start of 2L or 3L treatment	ddPCR (plasma)	29%	156/541
PEARL	AI-resistant HR+/HER2- mBC	Start of 2L or 3L treatment	ddPCR (plasma)	29%	164/557
PALOMA-3†	HR+/HER2- mBC that had relapsed or progressed on previous AI or tamoxifen monotherapy	Start of 2L or 3L treatment	ddPCR (plasma)	26%	114/445

Frequency of ESR1 mutations after using Aromatase Inhibitor

Turner Future Oncol 2023

Early Switch→ Biomarker Driven: PADA Trial





Updated Results: PFS1

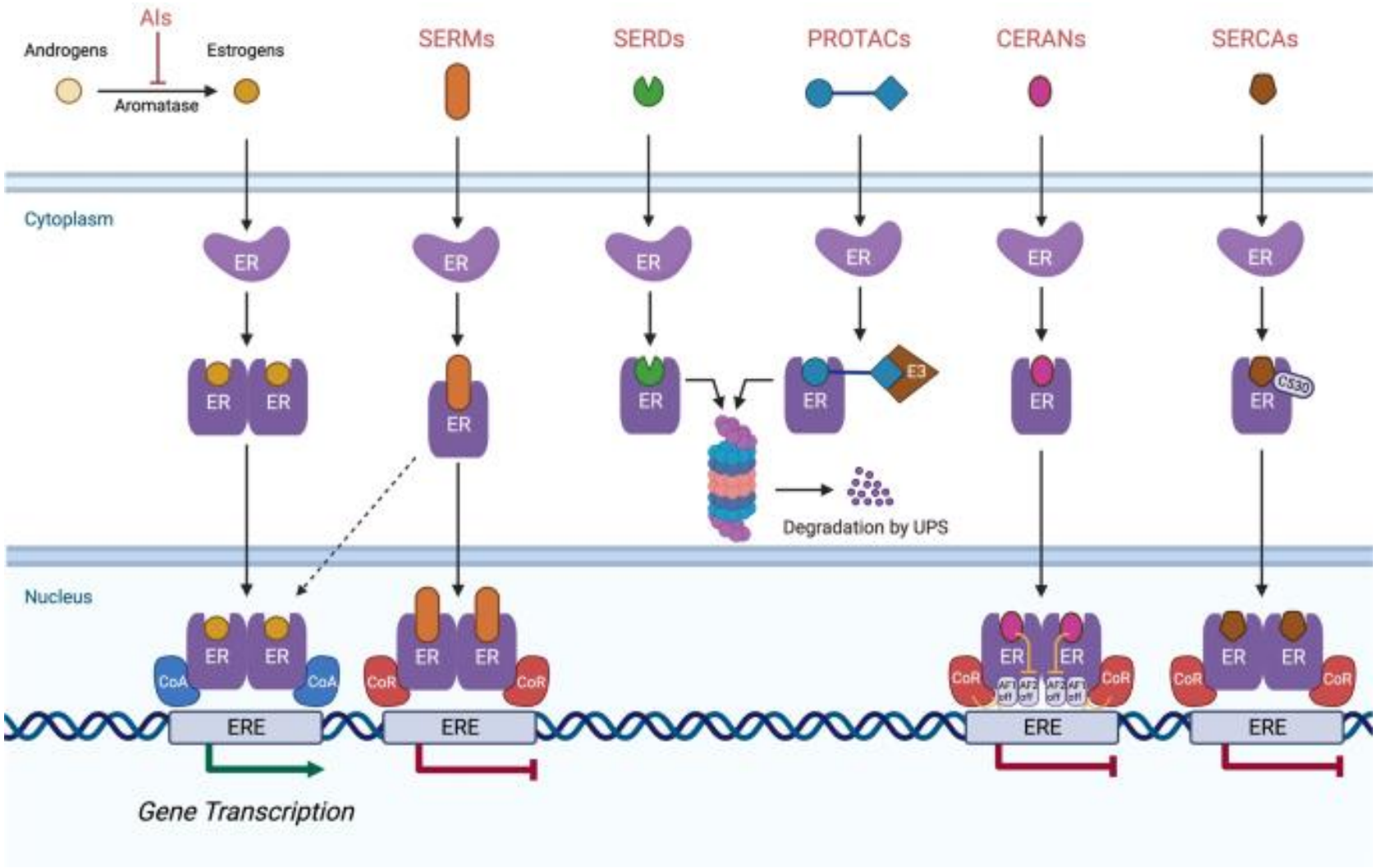
FUL+PAL mPFS: 12.8 months, 95%CI [9.3;14.7]

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

PFS HR= 0.54 [0.38;0.75]

FC Bidard, ASCO 2023

Development of Endocrine Therapies in Breast Cancer



Patel, R., Klein et al. *Breast Cancer* **9**, 20 (2023)

EMERALD Trial

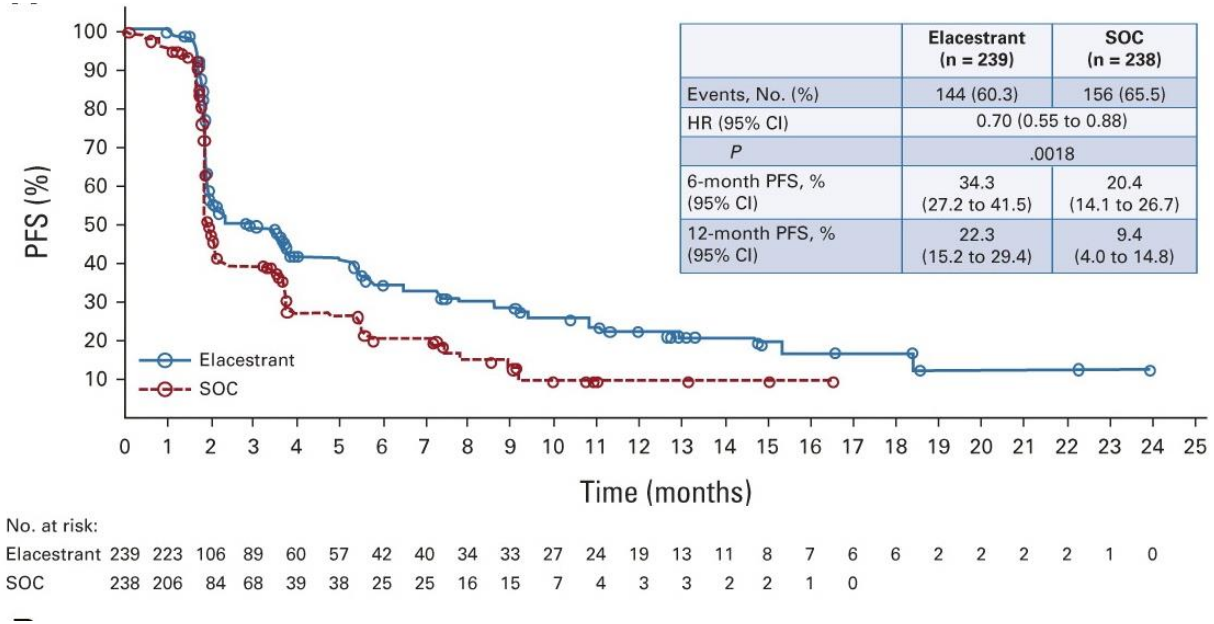
MBC with 1-2L ET, prior CDK4/6 ≤ 1 Ctx

- Elacestrant
- Investigator's choice : -AI, Fulvestrant

Endpoint	Elacestrant	Standard of Care	HR (95% CI)	*p* value
All patients	(*n* = 239)	(*n* = 238)		
Median PFS	2.79 months	1.91 months	0.697 (0.552-0.880)	.0018
Patients with *mESR1*-positive	(*n* = 115)	(*n* = 113)		
Median PFS	3.78 months	1.87 months	0.546 (0.387-0.768)	.0005

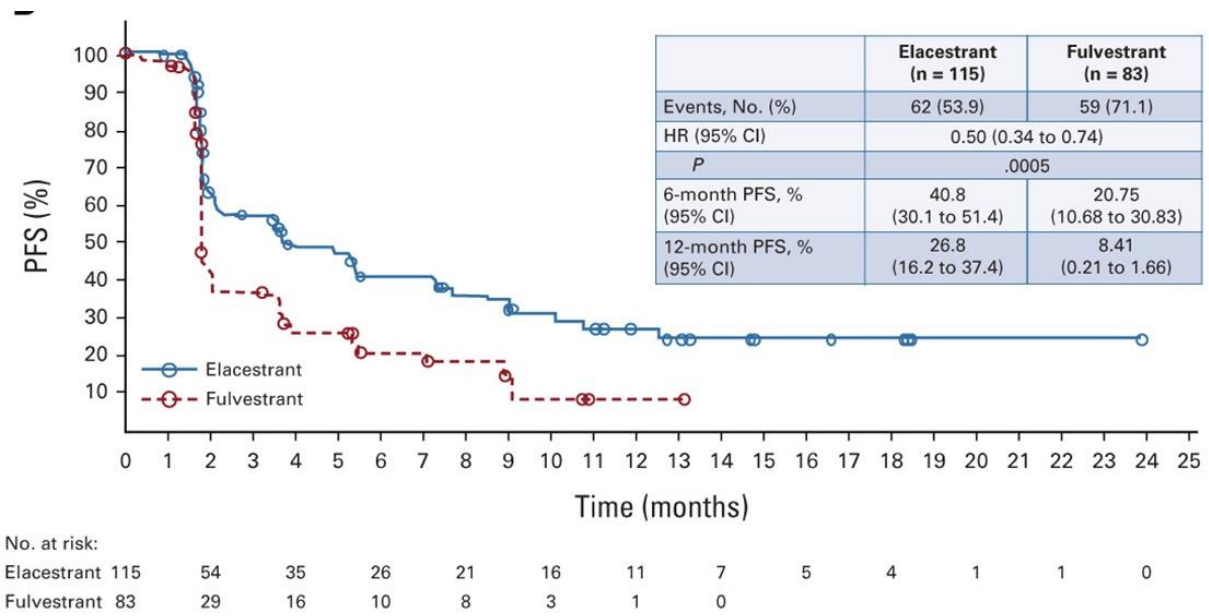
Significant PFS improvement versus SOC both in the overall population and in patients with *ESR1*

PFS in all patients vs SOC



	Elacestrant (n = 239)	SOC (n = 238)
Events, No. (%)	144 (60.3)	156 (65.5)
HR (95% CI)	0.70 (0.55 to 0.88)	
P	.0018	
6-month PFS, % (95% CI)	34.3 (27.2 to 41.5)	20.4 (14.1 to 26.7)
12-month PFS, % (95% CI)	22.3 (15.2 to 29.4)	9.4 (4.0 to 14.8)

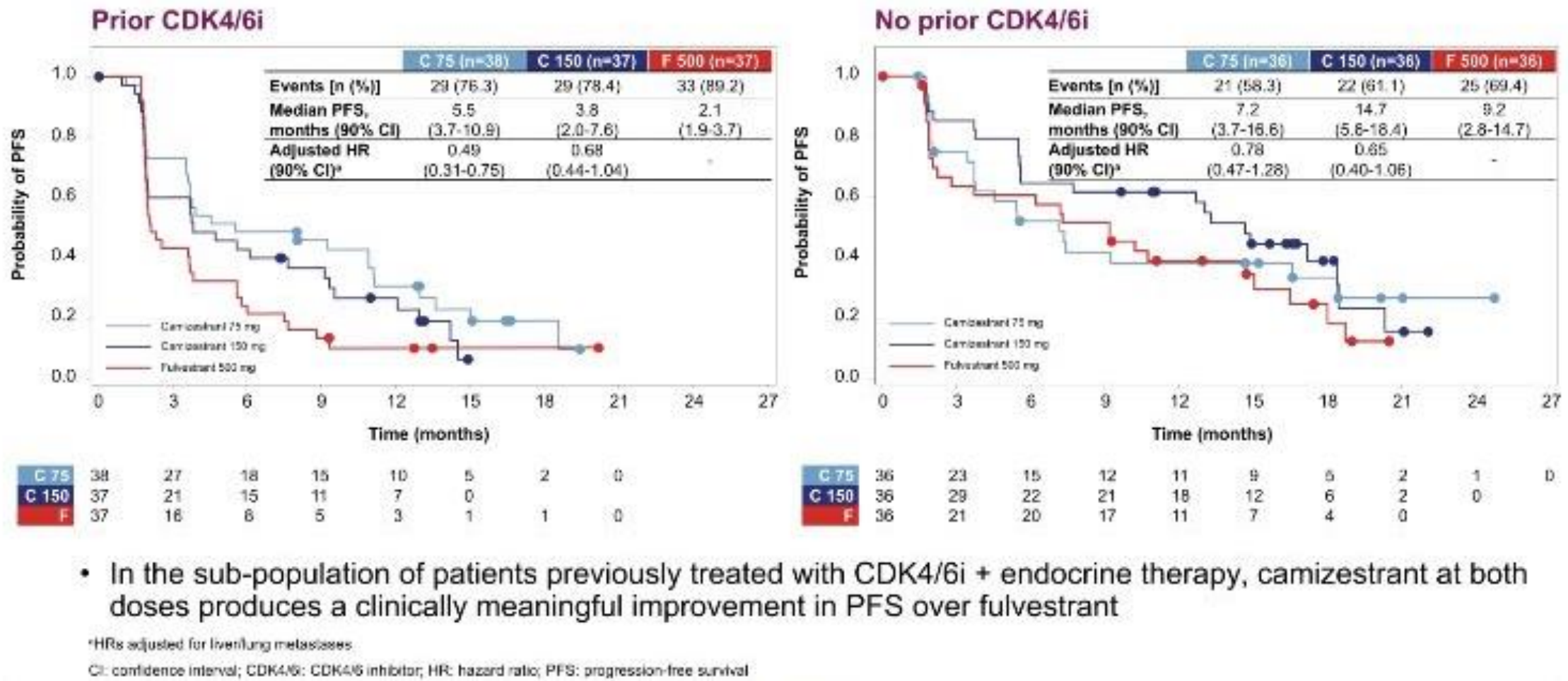
PFS in ESR1 + vs Fulvestrant



	Elacestrant (n = 115)	Fulvestrant (n = 83)
Events, No. (%)	62 (53.9)	59 (71.1)
HR (95% CI)	0.50 (0.34 to 0.74)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	20.75 (10.68 to 30.83)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.41 (0.21 to 1.66)

FC Bidard, JCO 2022

Serena-2 Trial Camizestrant



- 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

*HRs adjusted for liver/lung metastases

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

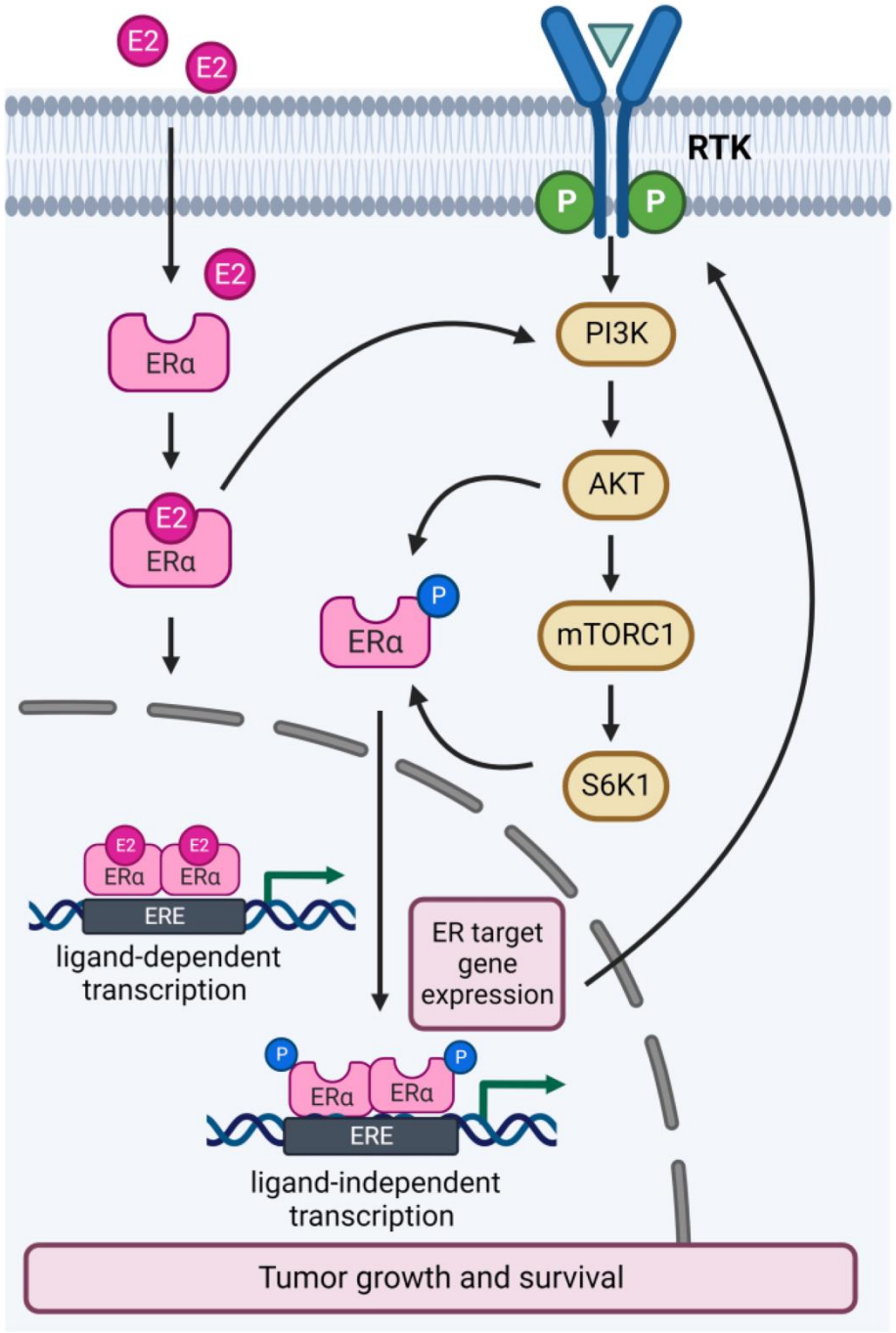
Oliveira M, et al SABCS 2022

Oral SERD Trials

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

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. Clinical Trials.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. acelERA 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

PI3K/AKT/mTOR Pathway



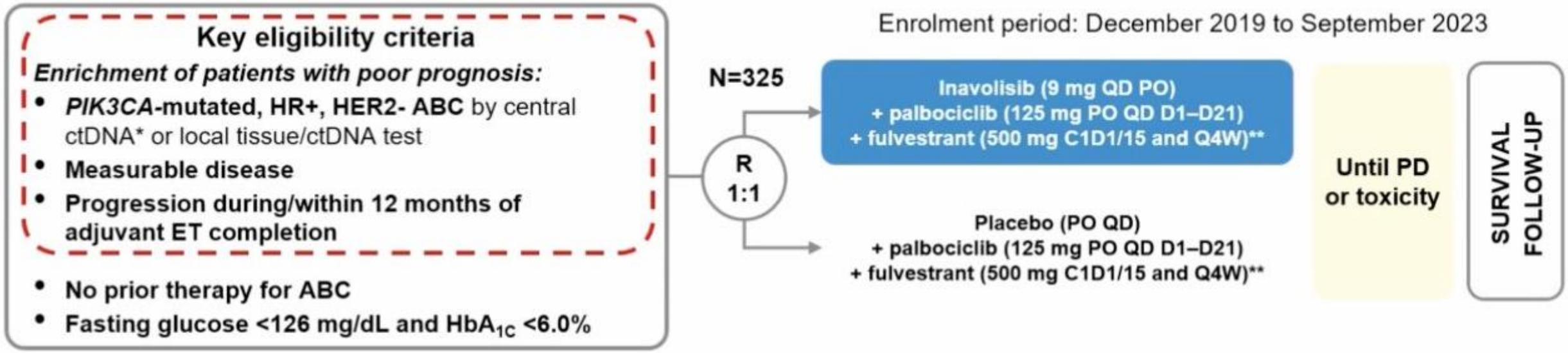
Alves, C.L.; Ditzel, H.J. *Int. J. Mol. Sci.* **2023**,

Targeting PIK3ca/AKT/mTOR Pathway

PI3K/AKT mTORi	Trial	Phase	Prior CDk4/6	Grade 3 Toxicity	mPFS months	mOS months
Alpelisib + Fulvestrant	Solar-1	3	6%	76% vs 35%	11 vs 5.7 mo	39.3 vs 31.4 mo
Capivasertib + Fulvestrant	Capitello-291	3	70%	16% vs 8%	7.2 vs 3.6 mo	immature
Everolimus + examestane	Bolero-2	3	0%	11% vs 1%	10.1 vs 4.3 mo	31 vs 26.6 mo NS

Mittal A, et al. Cancers **2023**

Inavolisib: new PIK on the block



Stratification factors:

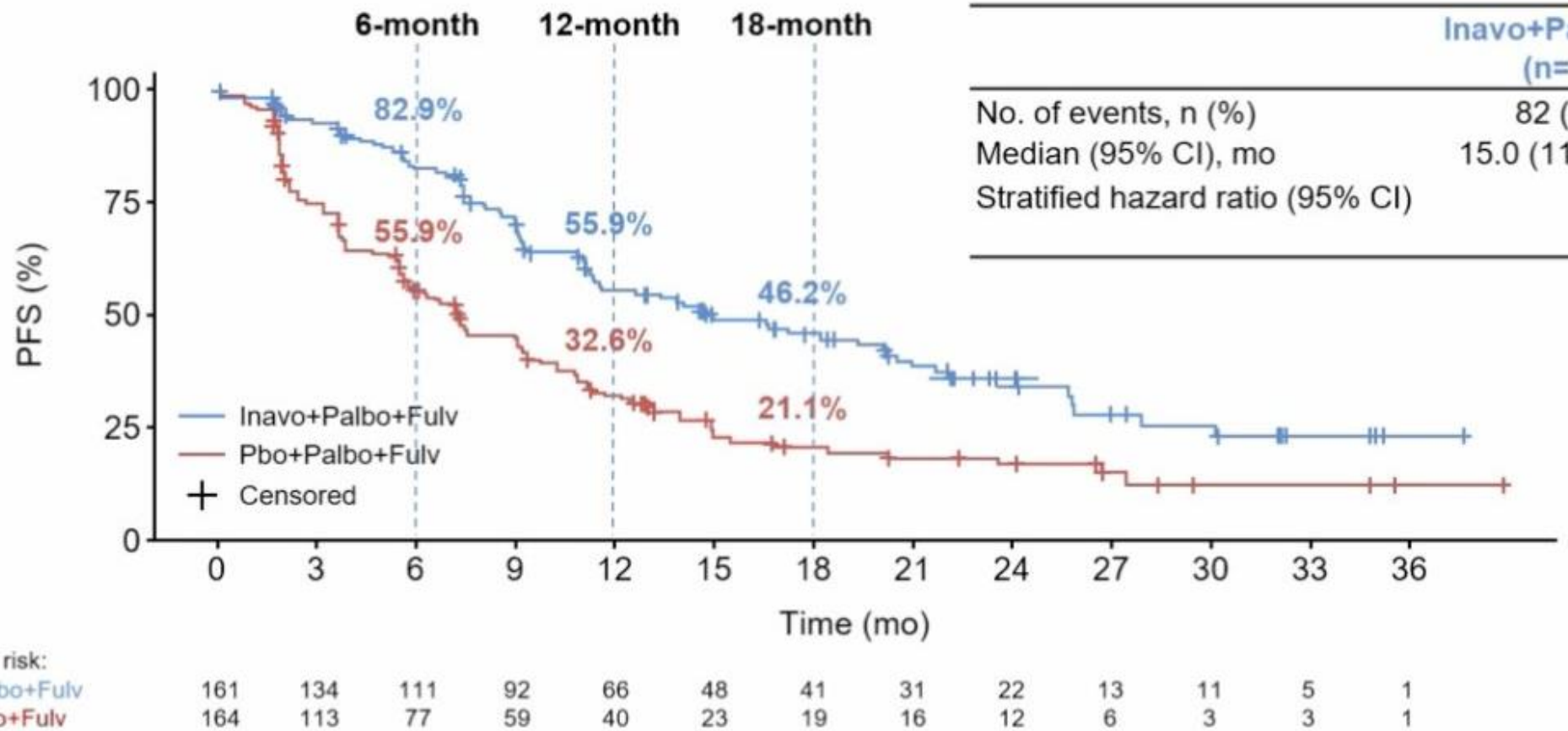
- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

Endpoints

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

Jhaveri K, et al SABCS 2023

Primary Endpoint: PFS



	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	

Most common adverse events
- Neutropenia 88% (80%)
- Stomatitis 51% (5%)
- Hyperglycemia 58% (5%)
- Diarrhea 48% (3%)
- Nausea 27%
- Rash 25%

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.

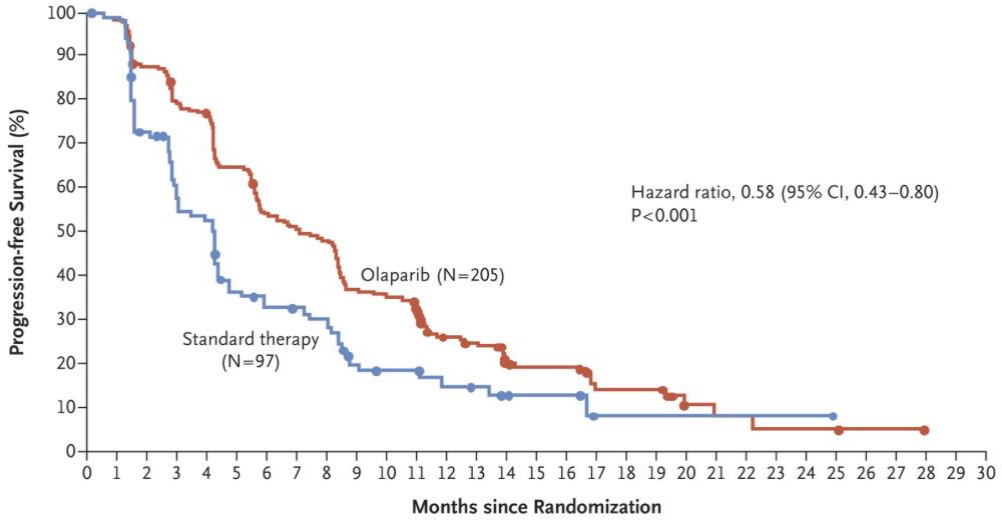
Jhaveri K, et al SABCS 2023

BRCA1/2

- Olaparib or Talazoparib (PARP inhibitor)
  - Approved for germline BRCA mutant HR+/HER2- MBC
- **OlympiAD1**: mPFS 7.0 mo with Olaparib vs 4.2 mo with TPC (HR 0.58, P <0.0009)
- **EMBRACA2**: mPFS 8.6 mo with Talazoparib vs 5.6 mo with TPC (HR 0.54, P <0.001)

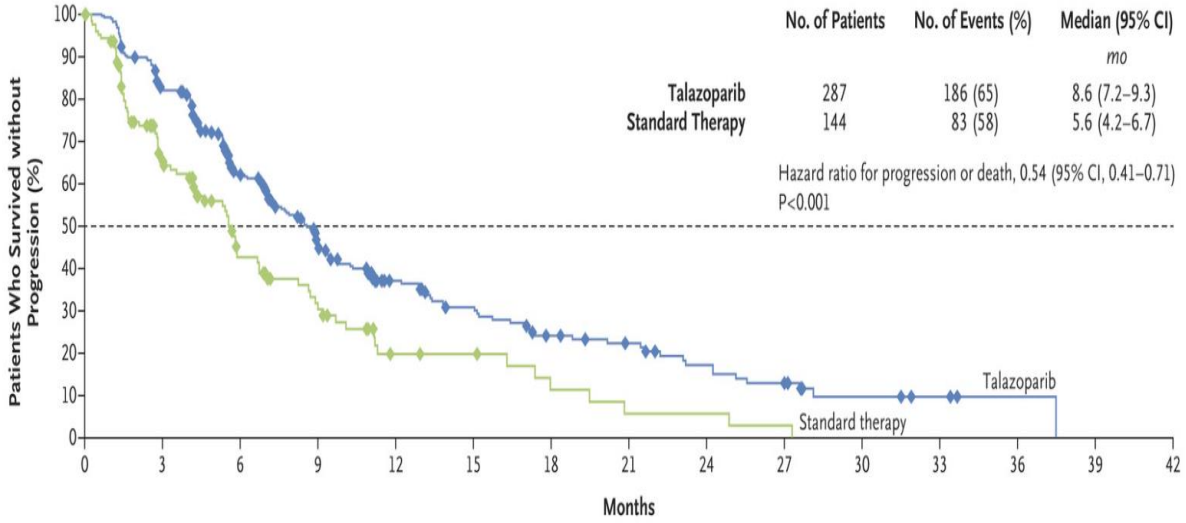
Germline testing should be done in all patients with MBC to determine eligibility to PARPi therapy

OlympiAD1 PFS



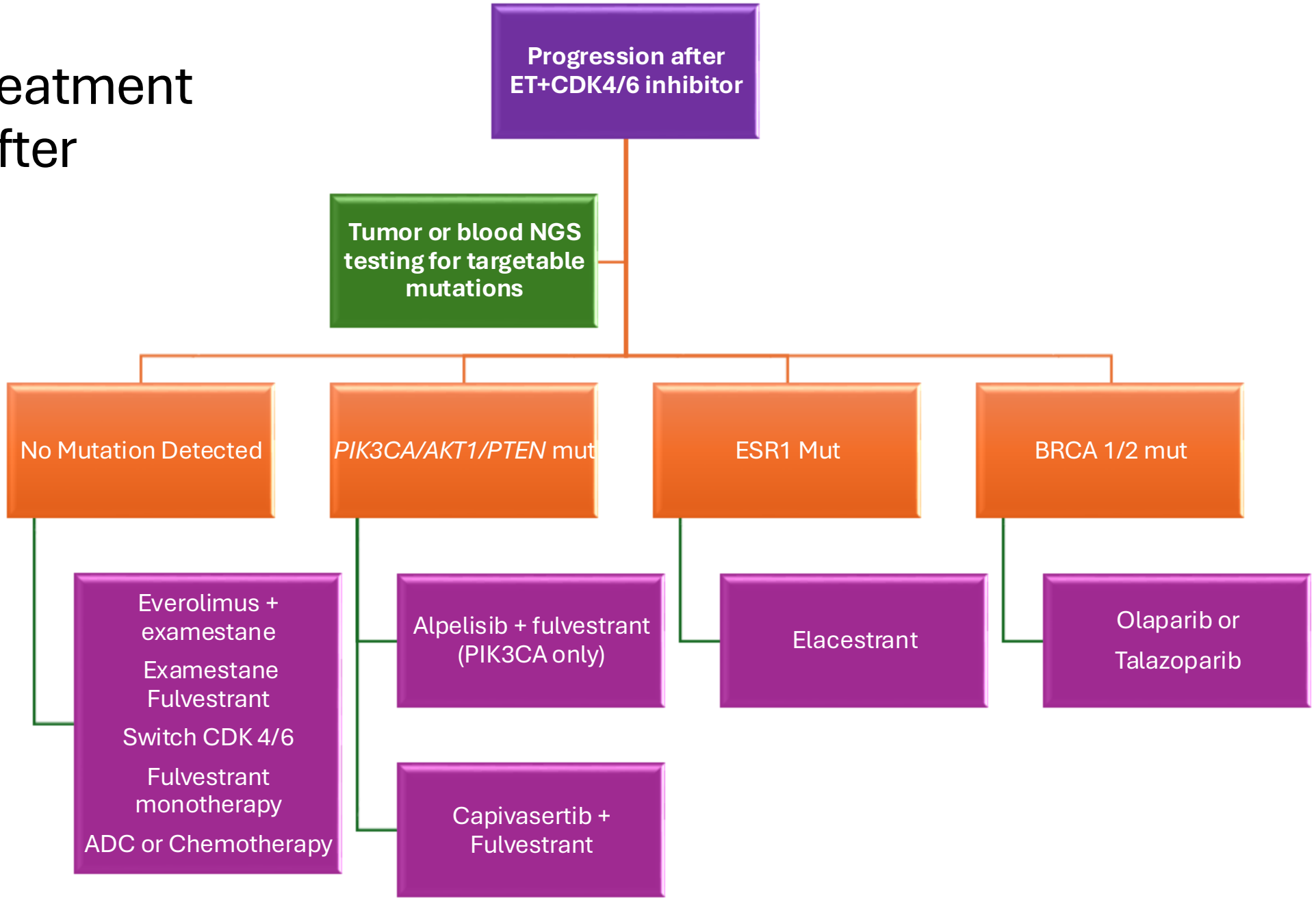
Robson M et al N Engl J Med 2017

EMBRACA PFS



Litton JK et al N Engl J Med 2018

Proposed Treatment Strategies After CDK4/6i



First-Line Preference:

CDK4/6i +ET is the preferred 1st line treatment approach.

Patient comorbidities, can guide the selection of the CDK4/6 agent.

However, strategic consideration should be given to certain patients who may potentially defer initiation of this combination.

Switching Strategies:

The continuation of CDK4/6 inhibitors beyond progression remains debated, as its benefits are not universally observed. When a treatment switch is necessary, optimizing both endocrine therapy (ET) and CDK4/6 inhibitors may lead to better outcomes.

Molecular Testing Guidance:

Molecular testing conducted upon disease progression holds promise in providing tailored guidance for the sequential administration of therapies, thereby optimizing treatment strategies.

Enhancements to Endocrine Therapy Backbone:

Advancements in the ET backbone, such as the integration of oral SERDs, PROTACs, and other innovative modalities, present opportunities for improving therapeutic efficacy and patient outcomes.