Hormone Therapy in Breast Cancer: New Directions

CALIFORNIA CANCER™ CONSORTIUM CONFERENCE

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Outline

I. Early-stage HR+, HER2 negative breast cancer
- Role of adjuvant CDK 4/6 inhibitors
  - NATALEE trial

II. Advanced HR+, HER2 negative breast cancer
- SONIA trial
- Overcoming endocrine resistance
  - Sequencing CDK 4/6 inhibitors
  - Oral SERDs
  - Targeting the PI3K/AKT/pTEN Pathway

EARLY BREAST CANCER

Current Data for Adjuvant CDK 4/6 Inhibitors

	PALLAS	PENELOPE-B	monarchE	NATALEE
No of patients	5760	1250	5637	5101
Eligibility	Anatomic stage II/III	Lack of pCR after NAC, CPS EG ≥ 3 or ≥ 2 with ypN+	≥ n2 or n1 w/at least G3 tumor, ≥ 5 cm, Ki-67 ≥ 20%	Included high risk N0 defined as G3 or G2 w/high genomic risk or Ki-67 ≥ 20%
Treatment	Palbociclib 2 years	Palbociclib 1 year	Abemaciclib 2 years	Ribociclib 3 years *400 mg
Discontinuation rate	42%	19.5%	27.7%	21%
IDFS	88.2% (palbociclib) vs 88.5% (endocrine therapy)	73.5% (palbociclib) vs 72.4% (endocrine therapy) at 4 years	92.2% (abemaciclib) vs 88.7% (endocrine therapy)	90.4% (ribociclib) vs 87.1% (endocrine therapy)
DRFS	89.3% vs 90.7%	-	93.8% vs 90.8%	90.8% vs 88.6%

Source: Advani, P. Exploring the Role of CDK4/6 Inhibitors in Early Breast Cancer. ASCOPubs (2021).

NATALEE Study Design[1,2]

- Adult patients with HR+/HER2− EBC
- Prior ET allowed up to 12 mo
- **Anatomical stage IIA**[a]
  - **N0** with:
    - Grade 2 and evidence of high risk:
      - Ki-67 ≥ 20%
      - Oncotype DX Breast Recurrence Score ≥ 26 *or*
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomical stage IIB**[a]
  - N0 or N1
- **Anatomical stage III**
  - N0, N1, N2, or N3

N = 5101[b]

R 1:1[c]

Ribociclib
400 mg/day
3 weeks on/1 week off for 3 y

NSAI
Letrozole or anastrozole[d] for ≥ 5 y **+ goserelin** in men and premenopausal women

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Randomization stratification
Anatomical stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
Receipt of prior (neo)adjuvant chemotherapy: yes vs no
Geographic location: North America/Western Europe/Oceania vs rest of world

Primary End Point
- iDFS using STEEP criteria

Secondary End Points
- Recurrence-free survival
- Distant disease–free survival
- OS
- PROs
- Safety and tolerability
- PK

Exploratory End Points
- Locoregional recurrence–free survival
- Gene expression and alterations in tumor ctDNA/ctRNA samples

[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from 10 Jan 2019 to 20 April 2021. [c] Open-label design. [d] Per investigator choice.
CT, chemotherapy; ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDFS, invasive disease-free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PAM50, prediction analysis of microarray 50; PK, pharmacokinetics; PRO, patient reported outcome; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.
1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03701334. Accessed April 6 2023. 2. Slamon DJ, et al. *J Clin Oncol.* 2019;37(15 suppl) [abstract TPS597].

NATALEE study design: unique features

- Adult patients with HR+/HER2− EBC
- Prior ET allowed up to 12 mo
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  - N1 with:
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400 mg/day
3 weeks on/1 week off
for 3 y

Rationale for broad population of patients
Patients with stage II and III HR+/HER2− EBC, including those with no nodal involvement, are at risk of disease recurrence up to decades after initial diagnosis[3,4]

Rationale for 400 mg RIB
To improve tolerability while maintaining efficacy

Rationale for 3-year treatment duration
Extended duration of treatment is crucial to prolong cell cycle arrest and drive more tumor cells into irreversible senescence[5-7]

tumor ctDNA/ctRNA samples

Randomization stratification
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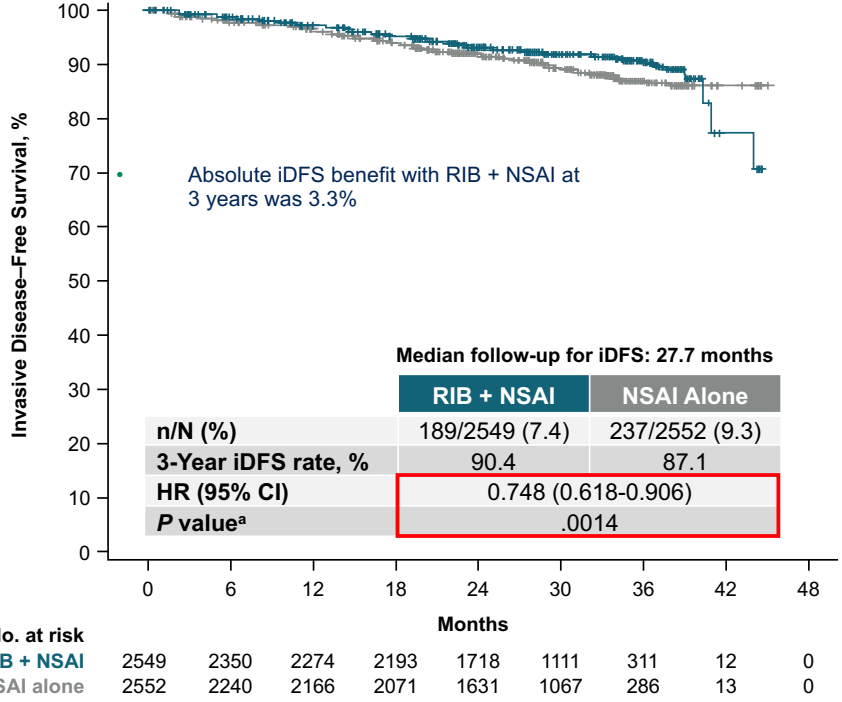
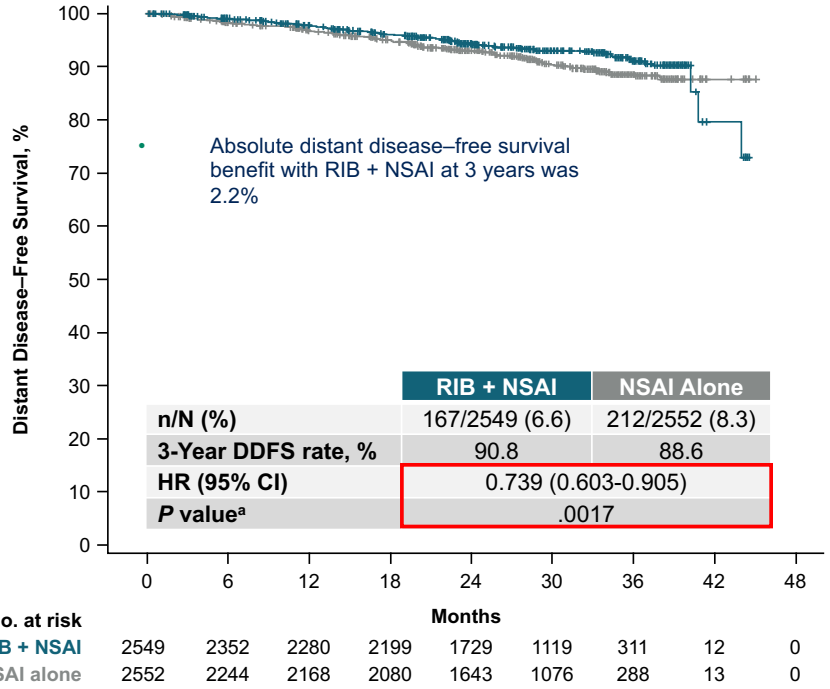
IDFS and DDFS



Median follow-up for iDFS: 27.7 months

	RIB + NSAI	NSAI Alone
n/N (%)	189/2549 (7.4)	237/2552 (9.3)
3-Year iDFS rate, %	90.4	87.1
HR (95% CI)	0.748 (0.618-0.906)	
P value[a]	.0014	

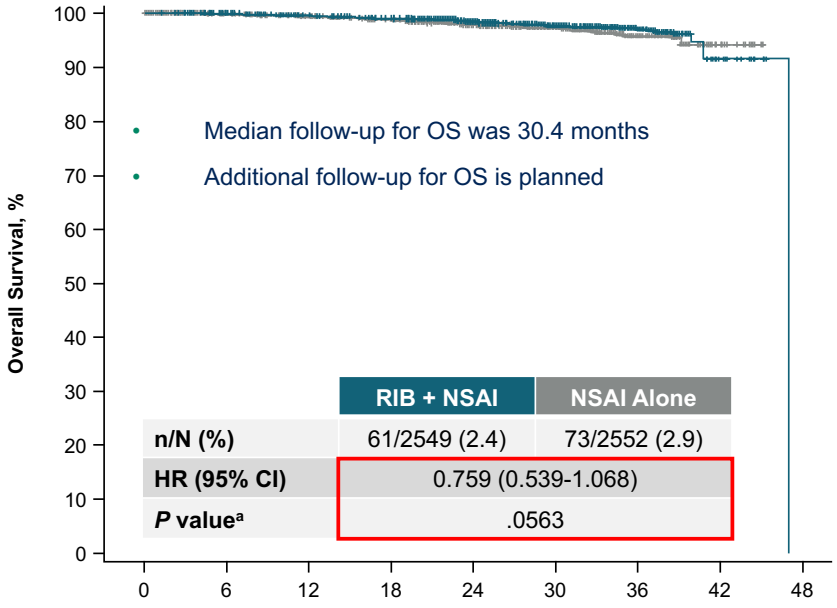
No. at risk									
RIB + NSAI	2549	2350	2274	2193	1718	1111	311	12	0
NSAI alone	2552	2240	2166	2071	1631	1067	286	13	0



	RIB + NSAI	NSAI Alone
n/N (%)	167/2549 (6.6)	212/2552 (8.3)
3-Year DDFS rate, %	90.8	88.6
HR (95% CI)	0.739 (0.603-0.905)	
P value[a]	.0017	

No. at risk									
RIB + NSAI	2549	2352	2280	2199	1729	1119	311	12	0
NSAI alone	2552	2244	2168	2080	1643	1076	288	13	0

Overall Survival and AEs



	RIB + NSAI n = 2524		NSAI Alone n = 2444	
AESIs, %	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Neutropenia[a]	62.1	43.8	4.5	0.8
Febrile neutropenia	0.3	0.3	0	0
Liver-related AEs[b]	25.4	8.3	10.6	1.5
QT interval prolongation[c]	5.2	1.0	1.2	0.5
ECG QT prolonged	4.2	0.2	0.7	0
ILD pneumonitis[d]	1.5	0	0.8	0.1
Other clinically relevant AEs,%				
Arthralgia	36.5	1.0	42.5	1.3
Nausea	23.0	0.2	7.5	0.04
Headache	22.0	0.4	16.5	0.2
Fatigue	21.9	0.7	12.7	0.2
Diarrhea	14.2	0.6	5.4	0.1
VTE	1.4	0.6	0.6	0.2

- The most frequent all-grade AEs (RIB + NSAI vs NSAI alone) leading to discontinuation were:
  - Liver-related AEs: 8.9% vs 0.1%
  - Arthralgia: 1.3% vs 1.9%
- Most of the AE discontinuations of RIB occurred early in treatment
  - Median time of these discontinuations was 4 months

AE, adverse event; AESI, adverse event of special interest; ILD, interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] This is a grouped term that combines neutropenia and neutrophil count decreased. [b] This is a grouped term that includes all preferred terms identified by standardized MedDRA queries for drug-related hepatic disorders. [c] This is a grouped term. [d] This is a grouped term that includes all preferred terms identified by standardized MedDRA queries for interstitial lung disease.

Summary NATALEE

- Ribociclib improves IDFS, DDFS in high-risk HR+/HER2- early breast cancer
  - High risk is defined more broadly- expanded definition to include any lymph node positive disease, node negative with high risk features
  - Administered at 400 mg for 3 years
  - Approximately 20% of patients completed 3 years at report - short term follow-up
- Ribociclib is not yet FDA approved in early breast cancer
- Who really needs adjuvant CDK 4/6 inhibitors beyond stage II or III patients?
  - ctDNA

Current Data for Adjuvant CDK 4/6 Inhibitors

Abemaciclib

- High risk disease - node positive
- 2 years, continuous dosing
- Same dosing in metastatic trials – 150 mg twice daily
- Adverse effects profile – diarrhea, fatigue, LFT increase
- Longer follow-up data available now including efficacy in subpopulations
- FDA approved in Oct 2021

Ribociclib

- High risk risk disease included any lymph node positive disease, and N0 high risk
- 3 years, intermittent dosing
- 400 mg (dose reduced from metastatic trials)
- Adverse effects profile - less incidence of QTc prolongation and neutropenia due to lower dose
- Shorter follow-up data available
- Not yet FDA approved for this indication

ADVANCED BREAST CANCER

CDK 4/6 Inhibitors for Metastatic Breast Cancer

	PALOMA-2	MONALESSA-2	MONARCH-3
Study Design	Phase III first line	Phase III first line	Phase III first line
Endocrine Partner	Letrozole	Letrozole	Letrozole or anastrozole
CDK 4/6 Inhibitor	Palbociclib	Ribociclib	Abemaciclib
Patients, N	666	668	493
HR	0.58	0.56	0.54
PFS, mos	24.8 vs. 14.5	25.3 vs. 16	28.2 vs. 14.8
ORR, %	55.3 vs. 44.4	52.7 vs. 37.1	59 vs. 44
OS, mos	53.9 vs 51.9	63.9 vs 51.4	67.1 vs 54.5

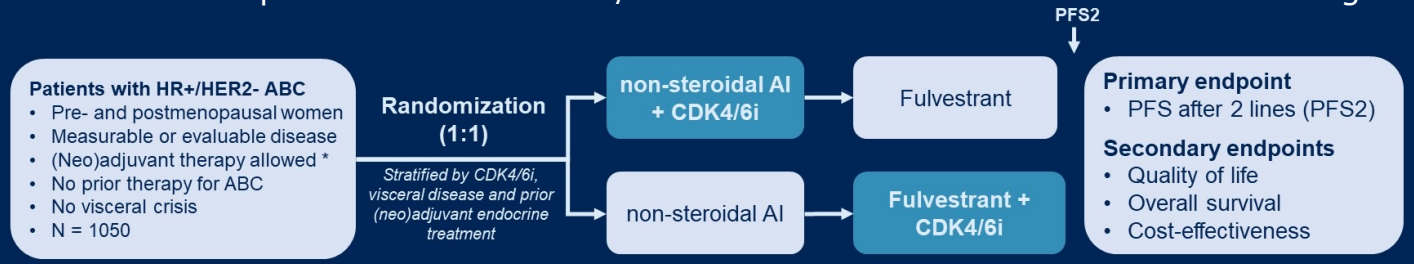
- Combination CDK 4/6i and endocrine therapy:
  - Higher risk of emergence of resistance mutation patterns
  - Increased toxicity and cost

HR = hazard ratio. PFS = progression-free survival. ORR = overall response rate. OS = overall survival

Source: Finn RS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med. 2016 Nov 17;375(20):1925-1936. doi: 10.1056/NEJMoa1607303. PMID: 27959613.
Hortobagyi GN, et al. Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer. N Engl J Med. 2022 Mar 10;386(10):942-950. doi: 10.1056/NEJMoa2114663. PMID: 35263519.
Goetz MP, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. J Clin Oncol. 2017 Nov 10;35(32):3638-3646. doi: 10.1200/JCO.2017.75.6155. Epub 2017 Oct 2. PMID: 28968163.

SONIA Trial Design

Aim: To compare the use of CDK 4/6 inhibitors in the first vs. second line setting



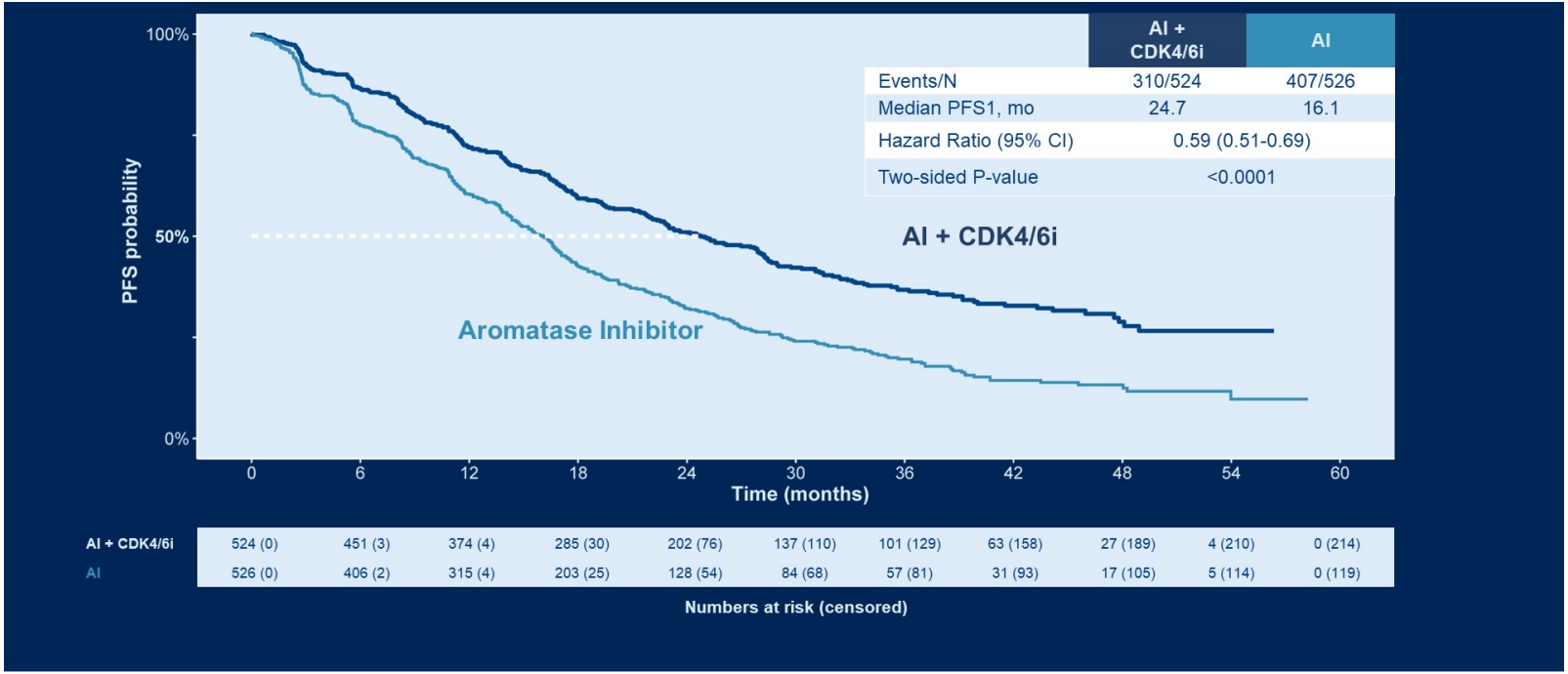
- Tumor assessments every 12 weeks
- PFS locally assessed per RECIST v1.1
- Primary analysis planned after 574 PFS2 events
  - 89% power to detect superiority according to ESMO MCBS (HR lower limit CI ≤0.65 and Δ ≥3 months) with two-sided α=5%[1]

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

SONIA Baseline Characteristics

		First-line CDK4/6i N=524	Second-line CDK4/6i N=526
Median age, years (range)		64 (24-88)	63 (25-87)
WHO PS, n (%)	0	257 (49)	257 (49)
	≥1	267 (51)	269 (51)
Menopausal status, n (%)	Pre- / perimenopausal	69 (13)	76 (14)
	Postmenopausal	455 (87)	450 (86)
Disease-free interval, n (%)	Newly diagnosed	182 (35)	182 (35)
	≤24 months	96 (18)	98 (19)
	>24 months	246 (47)	246 (47)
Prior (neo)adjuvant therapy, n (%)	Chemotherapy	212 (40)	210 (40)
	Endocrine therapy	258 (49)	254 (48)
Metastatic site, n (%)	Visceral disease	291 (56)	292 (56)
	Bone-only disease	91 (17)	91 (17)
Measurable disease, n (%)		315 (60)	312 (59)
Type of CDK4/6i, n (%)	Palbociclib	479 (91)	479 (91)
	Ribociclib	42 (8)	44 (8)
	Abemaciclib	3 (1)	3 (1)

SONIA Progression-free Survival in First Line



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PRESENTED BY: Prof. Gabe S. Sonke, MD, PhD

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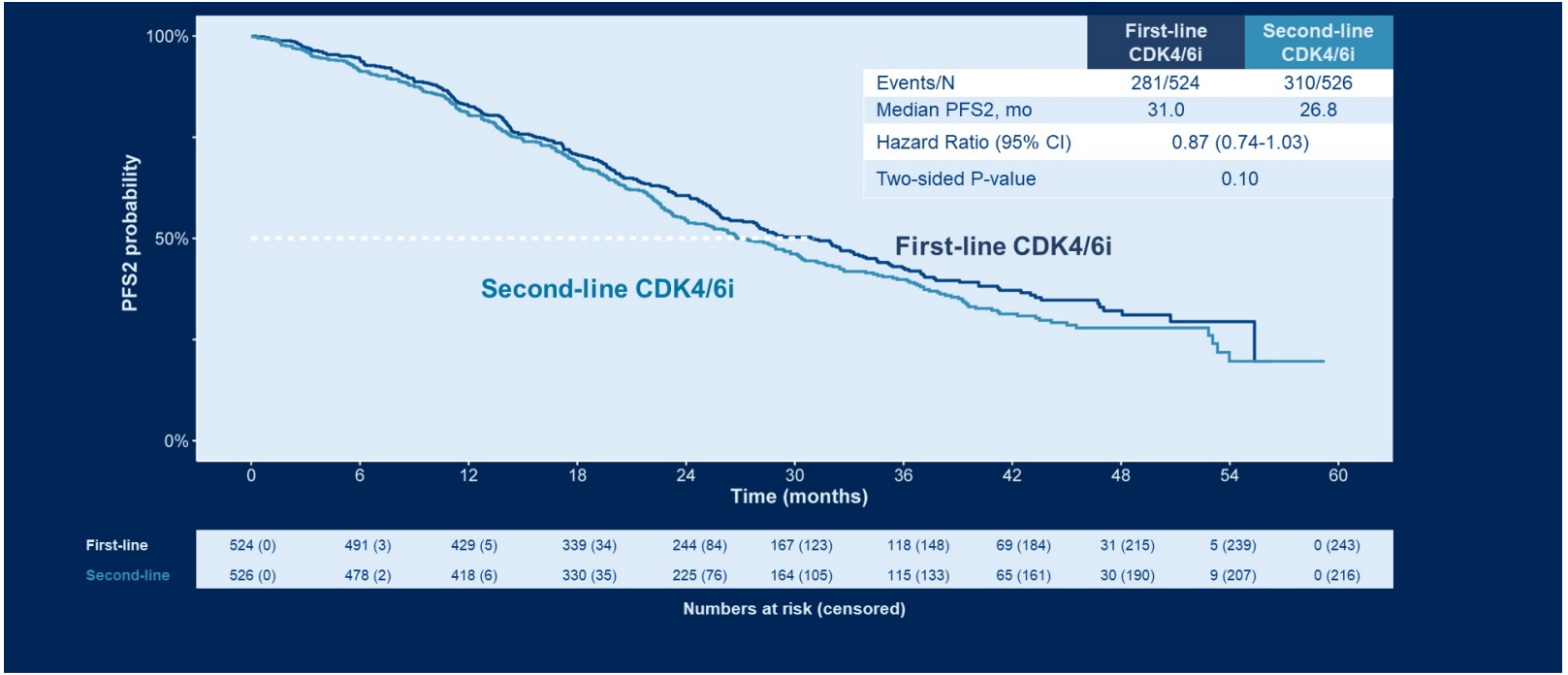
SONIA Primary Endpoint: PFS2



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

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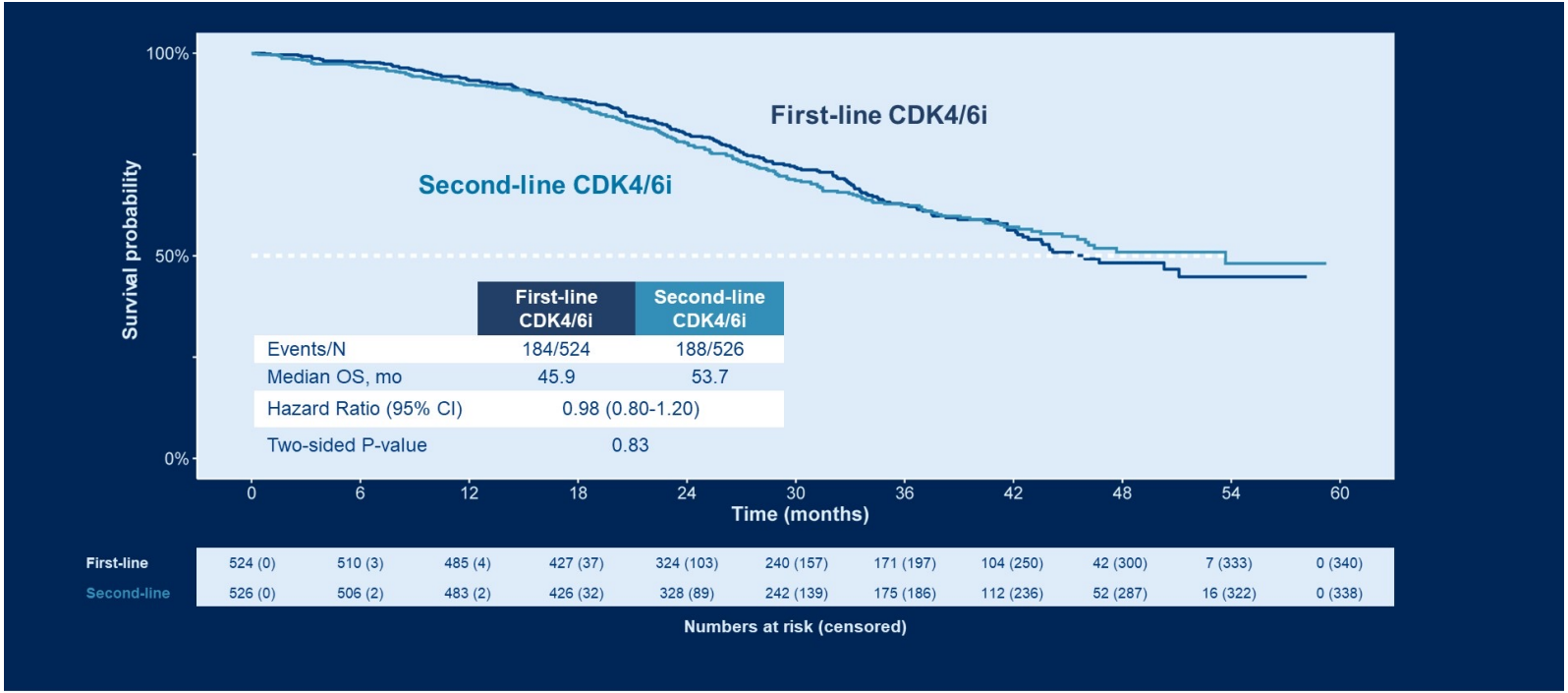
SONIA Overall Survival



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

PRESENTED BY: Prof. Gabe S. Sonke, MD, PhD

SONIA – Summary of Main Findings

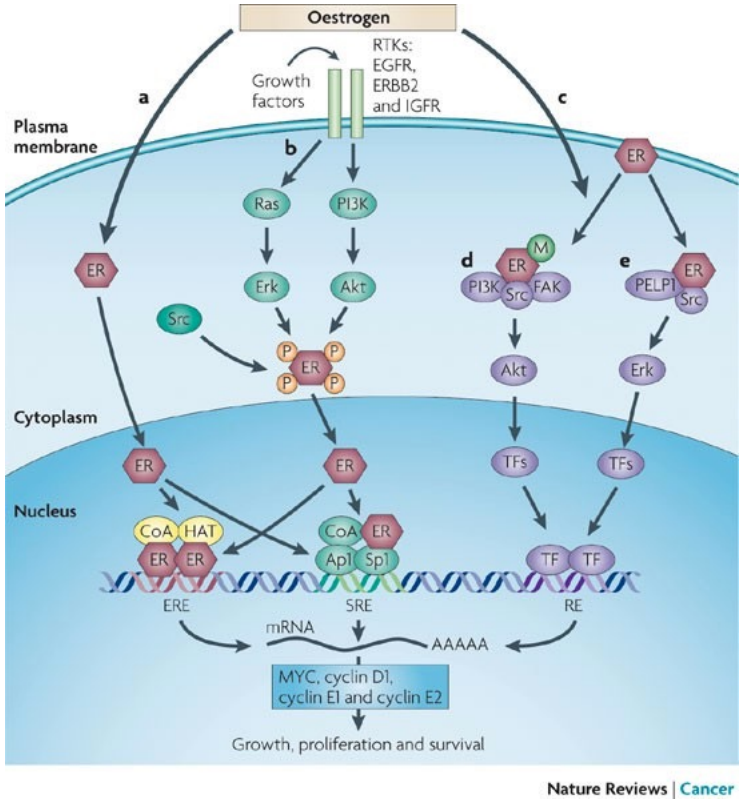
CDK4/6 inhibition in first-line compared to second-line

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

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

SONIA – Conclusions

- Do all patients need a CDK 4/6i in the first line setting?
  - How do we determine which subset of pts could be appropriate to not receive 1st line CDK 4/6i?
    - ctDNA?
- Does the CDK 4/6i matter?
  - 90% pts rec'd Palbociclib; OS data, adjuvant data for ribo and abema
- SONIA challenges the need for CDK 4/6i upfront for all pts

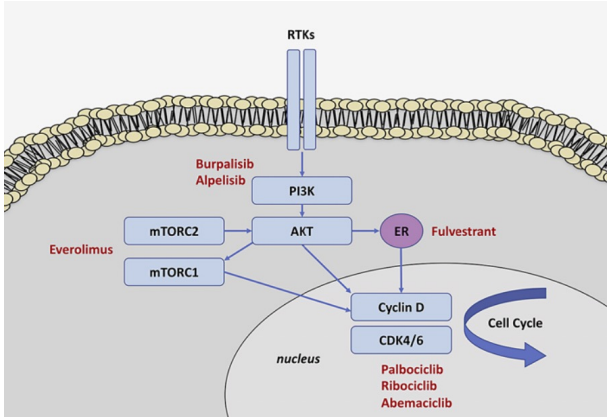


OVERCOMING ENDOCRINE RESISTANCE

Source: https://www.nature.com/articles/nrc2713

Overcoming Endocrine Resistance: What do we do post progression on CDK 4/6i?

- Shorter PFS, heterogeneity
- Primary endocrine resistance:
  - relapse within 2 years of adjuvant endocrine treatment for EBC
  - disease progression during the first 6 months of first-line endocrine therapy for ABC
- Secondary endocrine resistance:
  - relapse that occurs after at least 2 years of endocrine therapy and during or within the first year of completing adjuvant endocrine therapy for EBC
  - disease progression after more than 6 months of endocrine therapy for ABC
- NGS: ESR1, PIK3CA, AKT, PTEN
- Comorbidities
- Patient goals, toxicity



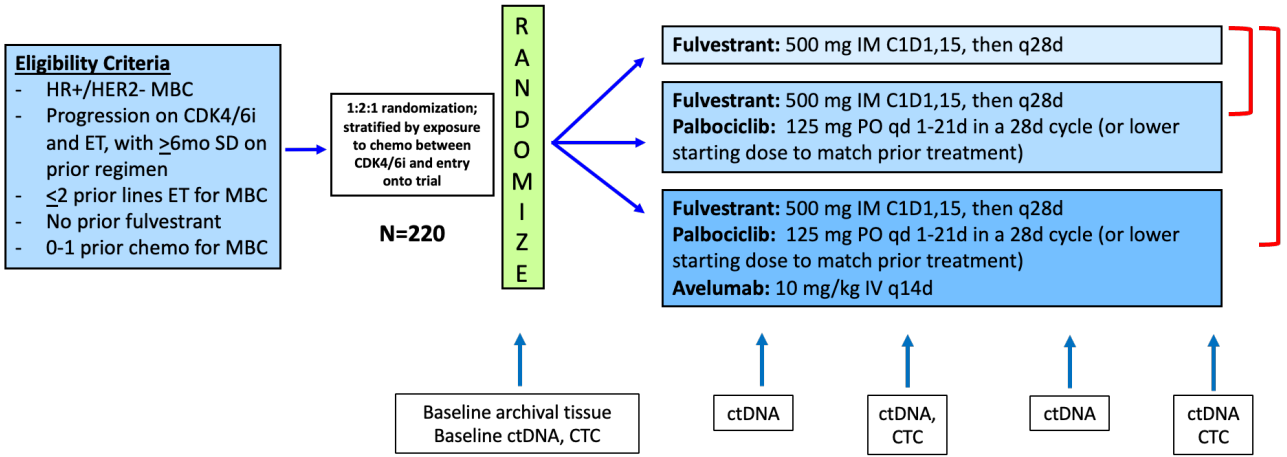
Source: Hartkopf A, D, Grischke E, -M, Brucker S, Y: Endocrine-Resistant Breast Cancer: Mechanisms and Treatment. Breast Care 2020;15:347-354. doi: 10.1159/000508675

Sequencing CDK 4/6 Inhibitors Post Progression

	MAINTAIN	PACE	PALMIRA
Patients (n)	120	220	198
1st line CDK 4/6 inhibitor	Palbociclib (84%)	Palbociclib (90%)	Palbociclib (100%)
Endo rx	Fulvestrant (83%)	Fulvestrant (100%)	Fulvestrant (90%)
Subsequent CDK 4/6i	Ribociclib	Palbociclib	Palbociclib
PFS endo rx and CDK 4/6i	5.3 months	4.6 months	4.9 months
PFS endo rx	2.8 months	4.8 months	3.6 months

PACE Trial Schema

- Designed to explore activity of continuation of CDK 4/6 inhibitor beyond progression, with a change of endocrine therapy to fulvestrant and to explore the addition of a PD-L1 inhibitor, avelumab



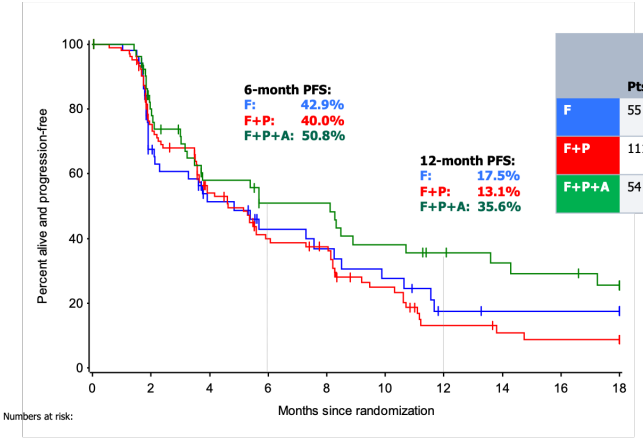
Primary objective: To compare PFS (RECIST-confirmed) for fulvestrant+palbociclib vs. fulvestrant alone

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

Source: Mayer et al, SABCS 2022.

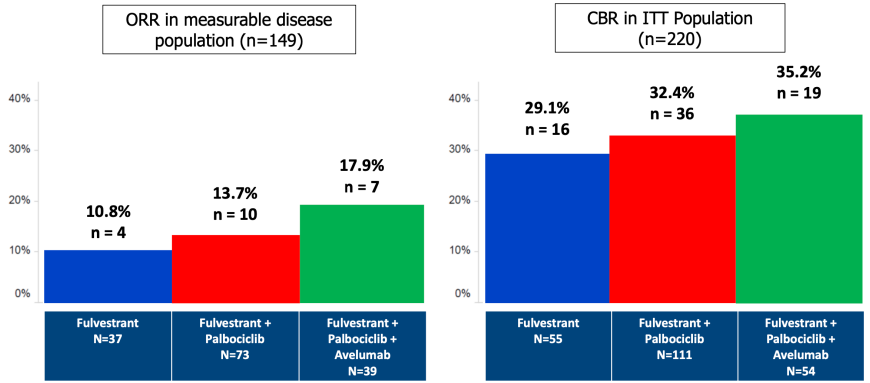
PACE PFS, ORR, CBR

PACE: Progression Free Survival ITT



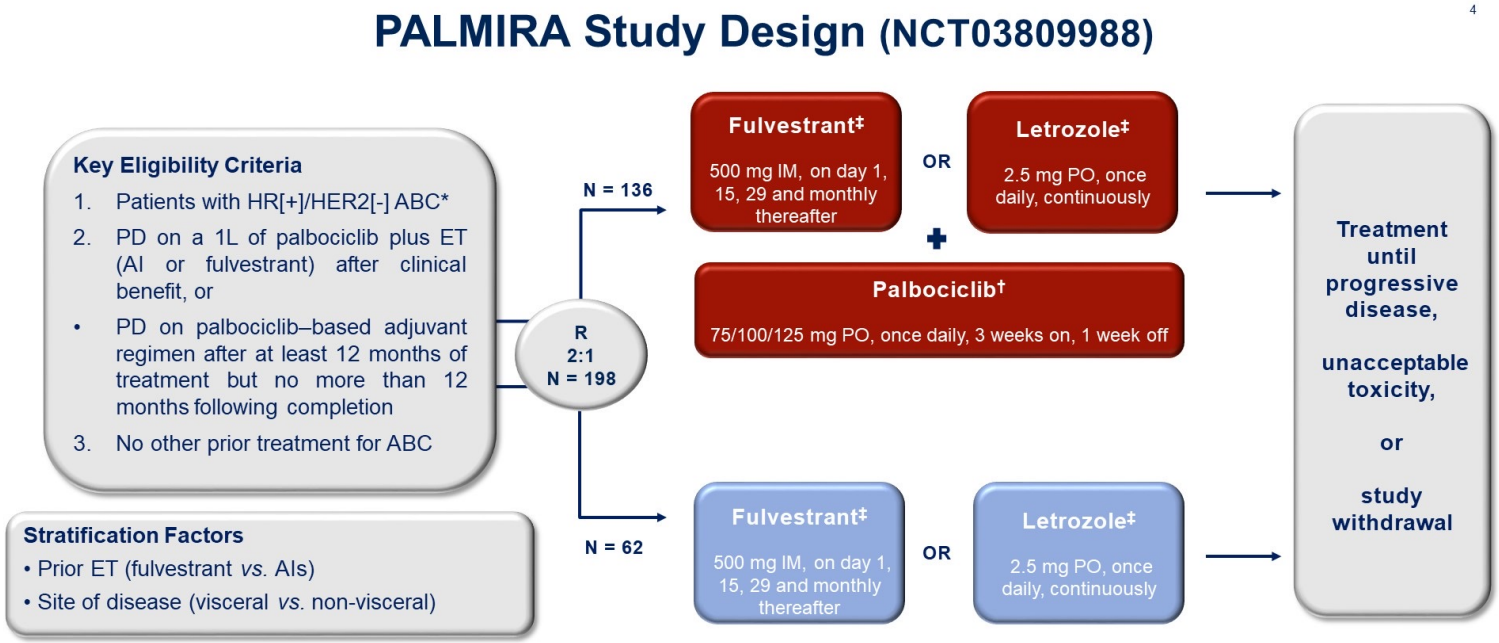
	Pts	PFS Events	Median PFS, mo (90% CI)	HR vs F (90% CI)	P-value
F	55	34	**4.8** (2.1, 8.2)	--	--
F+P	111	79	**4.6** (3.6, 5.9)	1.11 (0.74-1.66)	P=0.62
F+P+A	54	35	**8.1** (3.2, 10.7)	0.75 (0.47-1.20)	P=0.23

PACE: Response Endpoints



- Primary endpoint not met
- PFS 4.6 mos vs 4.8 mos w/ful alone
- Triplet nearly doubles PFS to 8.1 mos

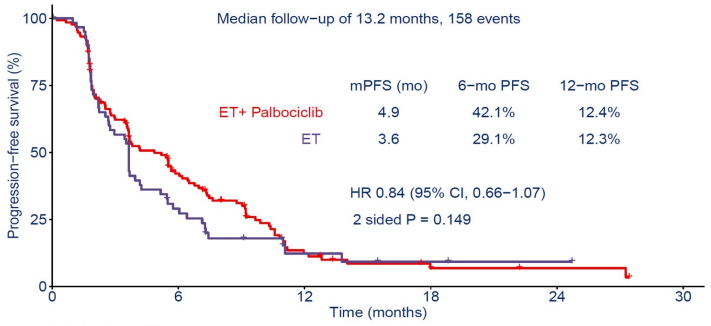
PALMIRA Trial Schema



1L: First–line; ABC: Advanced breast cancer; AI: Aromatase inhibitors; ET: Endocrine therapy; HER2[-]: Human Epidermal Growth Factor Receptor 2-negative; HR[+]: Hormone receptor-positive; IM: Intramuscular injection; PO: oral administration; PD: Progressive disease; R: Randomization.
*If pre-menopausal, ovarian function suppression method required.
†Palbociclib dose could be reduced until 75 mg. If a dose reduction below 75 mg is required, treatment must be discontinued.
‡Administration of endocrine therapy was chosen depending on the prior administered agent.

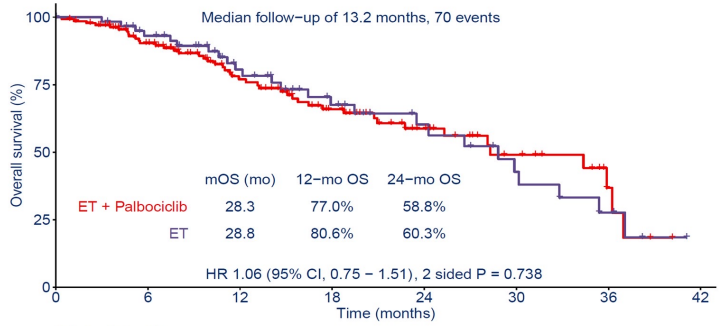
PALMIRA PFS and OS

Primary Objective: Investigator-assessed PFS (ITT Population)



CI: Confidence interval; HR: Hazard ratio; ITT: Intention to treat; mo: Months; mPFS: Median progression-free survival; PFS: Progression-free survival.

Overall Survival (ITT Population)



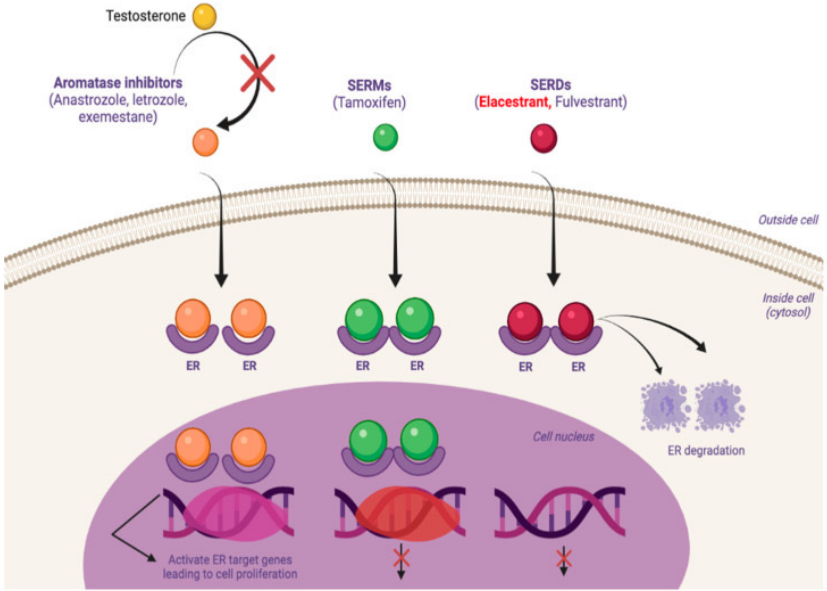
CI: Confidence interval; HR: Hazard ratio; ITT: Intention to treat; mo: Months; mOS: median Overall survival.

Is the story over for sequencing CDK 4/6 inhibitors after progression?

- Change of CDK 4/6 inhibitor
- Change of endocrine partner
  - Oral SERDs, ARV-471, SERM
- Subset of pts with disease that would likely respond to further CDK 4/6i
  - Biomarkers need to be identified
  - Differential impact based on mutation status noted on ctDNA
- Ongoing trials: postMONARCH, ELAINE-3, EMBER-3

Oral SERDs

- Resistance mechanism: *ESR1*
  - Estrogen receptor–dependent transcription and proliferation in the absence of estrogen
  - Predict resistance to AIs
- SERD: binds to estrogen receptor causing ER to be degraded/downregulated
- Elacestrant only FDA approved oral SERD
- Multiple oral SERDs in pipeline



Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8345926/

Treatment Landscape of Oral SERDs

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

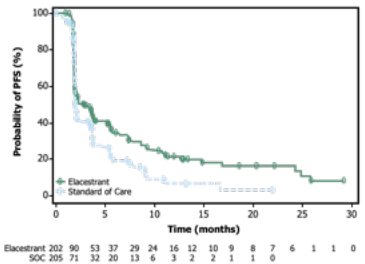
1. Bidard FC, et al. *J Clin Oncol.* 2022;40(28):3246-3256. 2. SERENA2. ClinicalTrials.gov identifier: NCT04214288. Accessed November 18, 2022, https://clinicaltrials.gov/ct2/show/NCT04214288; 3. EMBER-3. Clinical Trials.gov identifier: NCT04975308. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04975308; 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 TPS1100; 9. Martin Jimenez M, et al. *Ann Oncol.* 2022;33(7):S88-S121 (abstr 211MO).

Source: Kaklamani et al, SABCS 2022

EMERALD

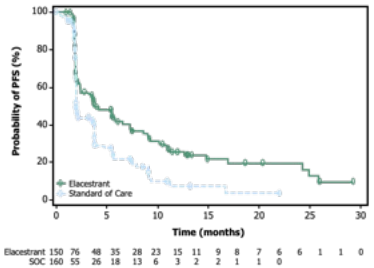
- Elacestrant monotherapy improves PFS in patients who had progressed on prior CDK 4/6i
  - Duration of CDK 4/6i associated w/PFS (longer duration, longer PFS on elacestrant vs SOC)
  - More pronounced in *ESR1* mutated tumors with at least 12 mos prior CDK 4/6i duration
- No new safety signals
  - Nausea mainly grade 1 or 2, no grade 4 events
    - Discontinuation rate 1.3% due to nausea
    - Any TRAE 3.4% discontinuation rate
    - No bradycardia
- **FDA approved elacestrant January 27, 2023 as monotherapy for *ESR1* mutant tumors!**
  - disease progression on one or two prior lines of endocrine therapy, including one line containing a CDK4/6 inhibitor

At least 6 mo CDK4/6i



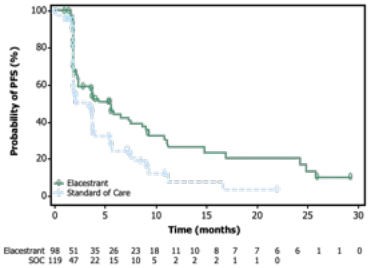
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**2.79** (1.94 - 3.78)	**1.91** (1.87 - 2.14)
PFS rate at 12 months, % (95% CI)	21.00 (13.57 - 28.43)	6.42 (0.75 - 12.09)
Hazard ratio (95% CI)	**0.688** (0.535 - 0.884)	

At least 12 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**3.78** (2.33 - 6.51)	**1.91** (1.87 - 3.58)
PFS rate at 12 months, % (95% CI)	25.64 (16.49 - 34.80)	7.38 (0.82 - 13.94)
Hazard ratio (95% CI)	**0.613** (0.453 - 0.828)	

At least 18 mo CDK4/6i

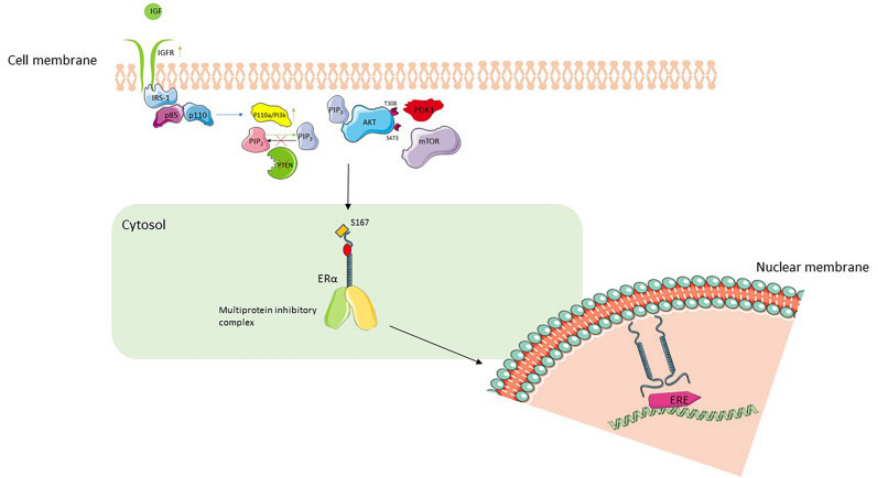


	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**5.45** (2.33 - 8.61)	**3.29** (1.87 - 3.71)
PFS rate at 12 months, % (95% CI)	26.70 (15.61 - 37.80)	8.23 (0.00 - 17.07)
Hazard ratio (95% CI)	**0.703** (0.482 - 1.019)	

Source: Kaklamani et al, SABCS 2022.

Targeting PI3K/AKT/pTEN Pathway

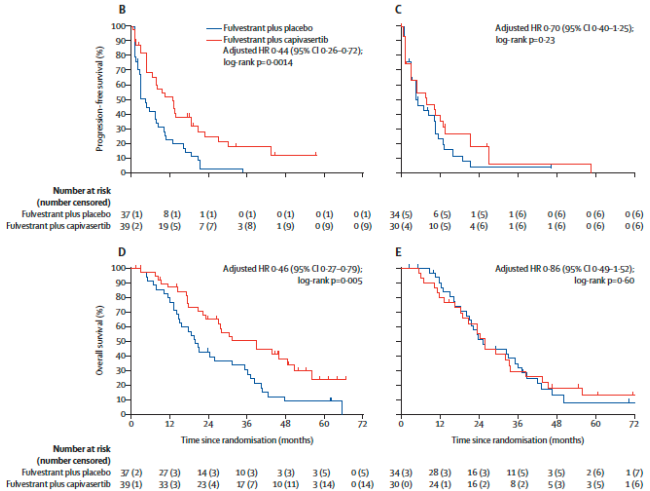
- Signaling in this pathway regulates growth, metabolism, and survival
- Overactivation occurs in 50% of HR+ ABC via activation mutations in PI3K and AKT pathways or inactivating mutations in pTEN pathway
- Alterations can be acquired from prior rx
- AKT pathway signaling can occur in the absence of genetic alterations
- Alpelisib and everolimus FDA approved
  - Prior to availability of CDK 4/6i



Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9400772/

Capivasertib

- Capivasertib is a potent, selective inhibitor of all three AKT isoforms (AKT1/2/3)
- FAKTION trial
  - Ph II trial of capi w/fulvestrant in AI resistant (no prior CDK 4/6i) HR+/HER2 neg ABC
  - PFS and OS benefit, more pronounced in *AKT* pathway altered tumors



Source: Howell SJ, Casbard A, Carucci M, Ingarfield K, Butler R, Morgan S, Meissner M, Bale C, Bezecny P, Moon S, Twelves C, Venkitaraman R, Waters S, de Bruin EC, Schiavon G, Foxley A, Jones RH. Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive, HER2-negative breast cancer (FAKTION): overall survival, updated progression-free survival, and expanded biomarker analysis from a randomised, phase 2 trial. Lancet Oncol. 2022 Jul;23(7):851-864. doi: 10.1016/S1470-2045(22)00284-4. Epub 2022 Jun 4. PMID: 35671774; PMCID: PMC9630162.

CAPItello-291

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

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

Capivasertib	400 mg twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks
Placebo	Twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks

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

Dual primary endpoints

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

Key secondary endpoints

Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

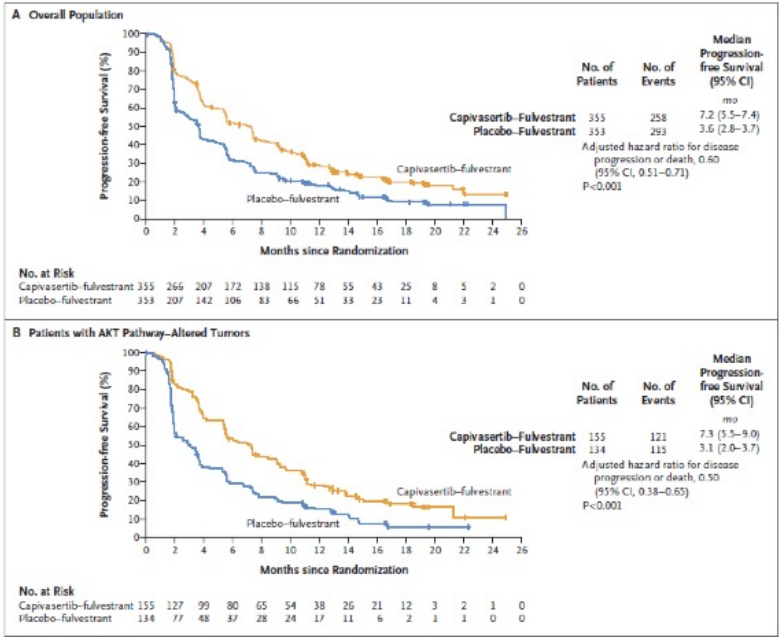
*HER2– was defined as IHC 0 or 1+, or IHC 2+/ISH–. *Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia v s Region 3: Asia. ABC, advanced (locally advanced [inoperable] or metastatic) breast cancer. Pre- or peri-menopausal women also received a luteinizing hormone-releasing hormone agonist for the duration of the study treatm ent˚*

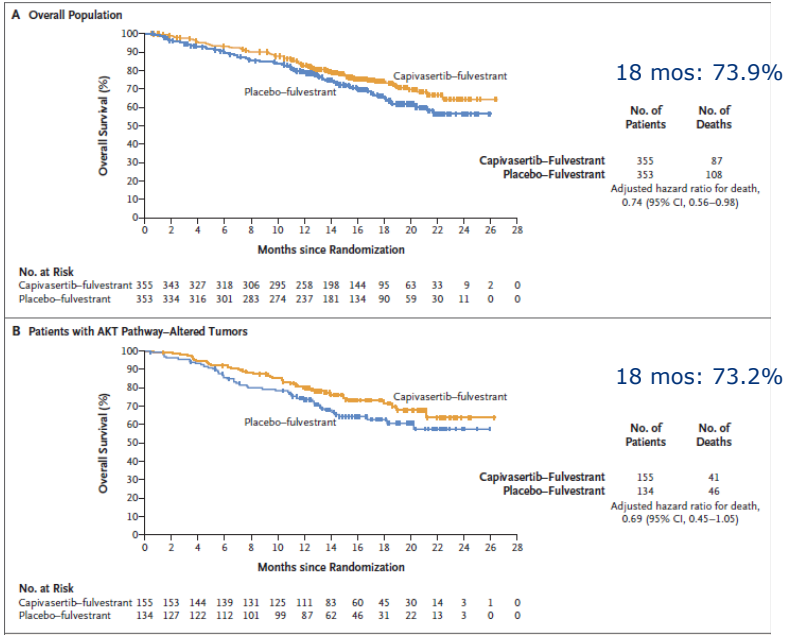
CAPItello-291: Characteristics

Site of metastases — no. (%)				
Bone only	51 (14.4)	52 (14.7)	25 (16.1)	16 (11.9)
Liver	156 (43.9)	150 (42.5)	70 (45.2)	53 (39.6)
Viscera	237 (66.8)	241 (68.3)	103 (66.5)	98 (73.1)
No. of previous therapies for advanced breast cancer — no. (%)§				
0	37 (10.4)	52 (14.7)	12 (7.7)	20 (14.9)
1	235 (66.2)	208 (58.9)	107 (69.0)	79 (59.0)
2	73 (20.6)	77 (21.8)	31 (20.0)	29 (21.6)
3	10 (2.8)	16 (4.5)	5 (3.2)	6 (4.5)
Hormone-receptor status — no. (%)¶				
ER-positive, PR-positive	255 (71.8)	246 (69.7)	116 (74.8)	101 (75.4)
ER-positive, PR-negative	94 (26.5)	103 (29.2)	35 (22.6)	31 (23.1)
ER-positive, with unknown PR status	5 (1.4)	4 (1.1)	4 (2.6)	2 (1.5)
Endocrine status — no. (%)‖				
Primary resistance	127 (35.8)	135 (38.2)	60 (38.7)	55 (41.0)
Secondary resistance	228 (64.2)	218 (61.8)	95 (61.3)	79 (59.0)
No. of previous endocrine therapies for advanced breast cancer — no. (%)				
0	39 (11.0)	54 (15.3)	13 (8.4)	20 (14.9)
1	287 (80.8)	252 (71.4)	131 (84.5)	96 (71.6)
2	29 (8.2)	47 (13.3)	11 (7.1)	18 (13.4)
Previous CDK4/6 inhibitor — no. (%)				
As neoadjuvant or adjuvant therapy	2 (0.6)	3 (1.1)	0	2 (1.5)
As therapy for advanced breast cancer	245 (69.0)	244 (69.1)	113 (72.9)	91 (67.9)
Previous chemotherapy — no. (%)				
As neoadjuvant or adjuvant therapy	180 (50.7)	170 (48.2)	79 (51.0)	67 (50.0)
As therapy for advanced breast cancer	65 (18.3)	64 (18.1)	30 (19.4)	23 (17.2)

Alteration; n (%)		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
Any AKT pathway alteration		**155 (43.7)**	**134 (38.0)**
PIK3CA	Any	116 (32.7)	103 (29.2)
	PIK3CA only	110 (31.0)	92 (26.1)
	PIK3CA and *AKT1*	2 (0.6)	2 (0.6)
	PIK3CA and *PTEN*	4 (1.1)	9 (2.5)
AKT1 only		18 (5.1)	15 (4.2)
PTEN only		21 (5.9)	16 (4.5)
Non-altered		**200 (56.3)**	**219 (62.0)**
AKT pathway alteration not detected		142 (40.0)	171 (48.4)
Unknown		58 (16.3)	48 (13.6)
No sample available		10 (2.8)	4 (1.1)
Preanalytical failure		39 (11.0)	34 (9.6)
Post analytical failure		9 (2.5)	10 (2.8)

CAPItello-291 PFS and OS





18 mos: 73.9% vs 65%

18 mos: 73.2% vs 62.9%

CAPItello-291 Safety

Table 2. Most Frequent Adverse Events in the Overall Population (Safety Population).*

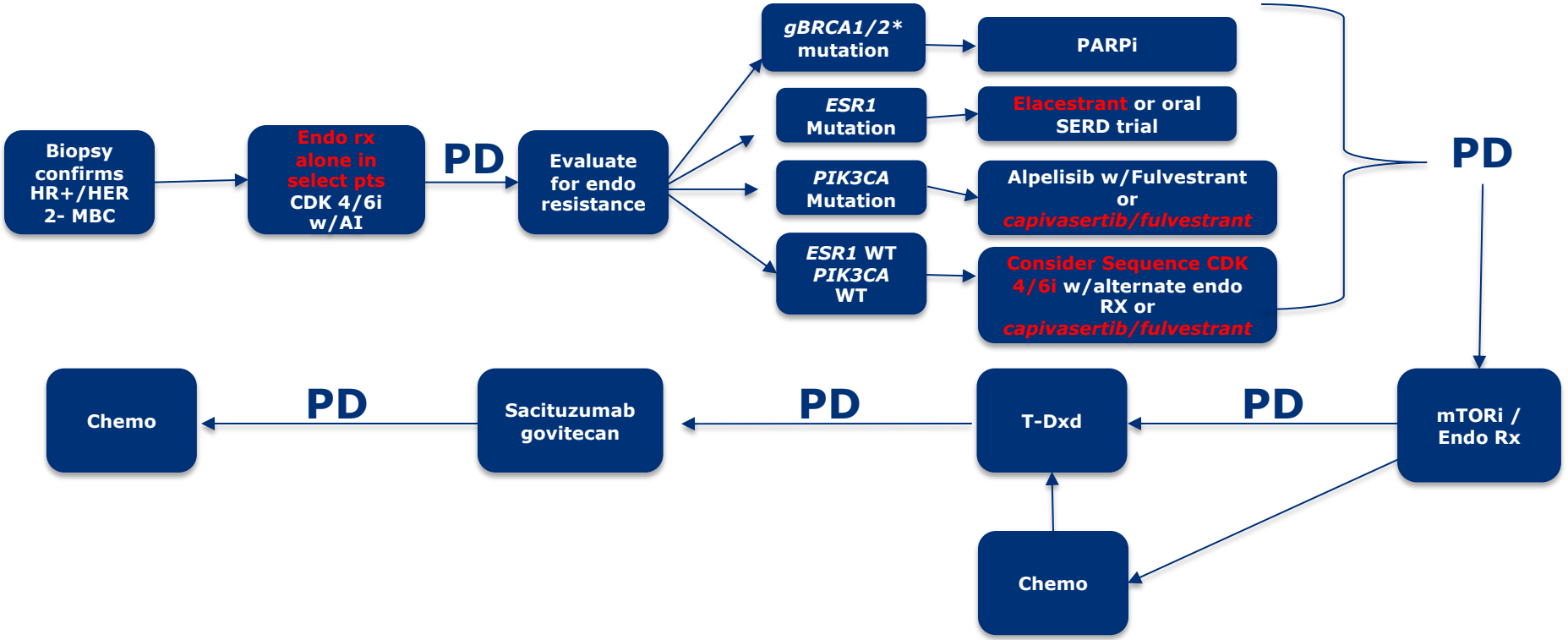
Event	Capivasertib–Fulvestrant (N=355)					Placebo–Fulvestrant (N=350)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
	number of patients (percent)									
Any adverse event	343 (96.6)	52 (14.6)	139 (39.2)	139 (39.2)	9 (2.5)	288 (82.3)	115 (32.9)	118 (33.7)	44 (12.6)	10 (2.9)
Diarrhea	257 (72.4)	164 (46.2)	60 (16.9)	33 (9.3)	0	70 (20.0)	60 (17.1)	9 (2.6)	1 (0.3)	0
Rash†	135 (38.0)	57 (16.1)	35 (9.9)	43 (12.1)	0	25 (7.1)	19 (5.4)	5 (1.4)	1 (0.3)	0
Nausea	123 (34.6)	85 (23.9)	35 (9.9)	3 (0.8)	0	54 (15.4)	42 (12.0)	10 (2.9)	2 (0.6)	0
Fatigue	74 (20.8)	49 (13.8)	23 (6.5)	2 (0.6)	0	45 (12.9)	35 (10.0)	8 (2.3)	2 (0.6)	0
Vomiting	73 (20.6)	54 (15.2)	13 (3.7)	6 (1.7)	0	17 (4.9)	10 (2.9)	5 (1.4)	2 (0.6)	0
Headache	60 (16.9)	47 (13.2)	12 (3.4)	1 (0.3)	0	43 (12.3)	33 (9.4)	8 (2.3)	2 (0.6)	0
Decreased appetite	59 (16.6)	37 (10.4)	21 (5.9)	1 (0.3)	0	22 (6.3)	11 (3.1)	9 (2.6)	2 (0.6)	0
Hyperglycemia	58 (16.3)	24 (6.8)	26 (7.3)	7 (2.0)	1 (0.3)	13 (3.7)	8 (2.3)	4 (1.1)	1 (0.3)	0
Stomatitis	52 (14.6)	24 (6.8)	21 (5.9)	7 (2.0)	0	17 (4.9)	15 (4.3)	2 (0.6)	0	0
Asthenia	47 (13.2)	29 (8.2)	14 (3.9)	4 (1.1)	0	36 (10.3)	31 (8.9)	3 (0.9)	2 (0.6)	0
Pruritus	44 (12.4)	32 (9.0)	10 (2.8)	2 (0.6)	0	23 (6.6)	19 (5.4)	4 (1.1)	0	0
Anemia	37 (10.4)	15 (4.2)	15 (4.2)	7 (2.0)	0	17 (4.9)	4 (1.1)	9 (2.6)	4 (1.1)	0
Urinary tract infection	36 (10.1)	8 (2.3)	23 (6.5)	5 (1.4)	0	23 (6.6)	2 (0.6)	21 (6.0)	0	0

SAE:
-16.1% vs 8%
Discontinuation rate
-9.3% vs 0.6%
Dose interruption:
-34.9% vs 10.3%
Dose reduction:
-19.7% vs 1.7%

CAPItello-291 Summary

- Capivasertib with Fulvestrant improves PFS in the overall and AKT altered population
  - Activity in non-AKT pathway-altered tumors
  - Activity post progression on CDK 4/6i
- Safety: diarrhea and rash most common
  - Hyperglycemia mainly grade 1 and 2
- Capivasertib ongoing investigation, as well other *PIK3CA* inhibitors

Management HR+/HER2 Negative MBC



- ✓ Continuously assess for clinical trial eligibility
- ✓ * can consider use for other germline HRR deficiencies

Questions?