

Consensus or Controversy? Documenting and Discussing Investigators' Approaches to the Use of Oral SERDs and Agents Targeting the PI3K/AKT/mTOR Pathway in Breast Cancer

Sunday, May 31, 2026

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Sara A Hurvitz, MD, FACP

Erica Mayer, MD, MPH, FASCO

Joyce O'Shaughnessy, MD

Nicholas Turner, MD, PhD

Moderator

Sara M Tolaney, MD, MPH

Faculty



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Smith Family Endowed Chair in Women's Health
Senior Vice President, Clinical Research Division
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Moderator

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Contributing Clinical Investigator



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Dr Hurvitz — Disclosures

Faculty

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Consulting Agreements	ALX Oncology, Bayer HealthCare Pharmaceuticals, BeOne, Blueprint Medicines, Ellipses Pharma, EMBioSys, Genentech, a member of the Roche Group, Jazz Pharmaceuticals Inc, Myricx Bio
Contracted Research	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Menarini Group, Novartis, Stemline Therapeutics Inc
Data and Safety Monitoring Boards/Committees	Atossa Therapeutics (paid to institution), Roche Laboratories Inc (paid to UW)
Nonrelevant Financial Relationships	Alliance for Clinical Trials in Oncology Foundation, InClin, Quantum Leap Healthcare Collaborative, ROMTech (Stocks for orthopedic device for postop pts; not cancer related)

Dr Mayer — Disclosures Faculty

Consulting Agreements	Aktis Oncology, AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, Lilly, Novartis
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Dr O'Shaughnessy — Disclosures Faculty

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Dr Turner — Disclosures Faculty

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Dr Tolaney — Disclosures

Moderator

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Contracted Research	AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Daiichi Sankyo Inc, Exelixis Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Jazz Pharmaceuticals Inc, Lilly, Menarini Group, Merck, NanoString Technologies, Novartis, OncoPep, Pfizer Inc, Seagen Inc, Stemline Therapeutics Inc
Travel	Arvinas, AstraZeneca Pharmaceuticals LP, Gilead Sciences Inc, Jazz Pharmaceuticals Inc, Lilly, Pfizer Inc, Roche Laboratories Inc

Dr Kaklamani — Disclosures

Contributing Clinical Investigators

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Lilly, Menarini Group, Novartis, Pfizer Inc
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Research To Practice President Neil Love, MD — Disclosures

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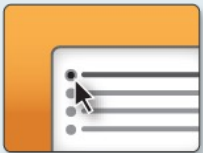
This educational activity contains discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.

Clinicians in the Meeting Room

Networked iPads are available.



Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.



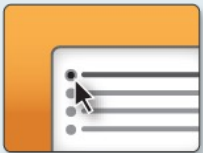
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For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based program. An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, www.ResearchToPractice.com



Friday May 29	Gastroesophageal Cancers 11:30 AM – 1:00 PM CT (12:30 PM – 2:00 PM ET)
	Non-Small Cell Lung Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
	Chronic Lymphocytic Leukemia 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
	Colorectal Cancer 6:30 PM – 8:00 PM CT (7:30 PM – 9:00 PM ET)
Saturday May 30	Ovarian Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Prostate Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Small Cell Lung Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Sunday May 31	Oral SERDs and Agents Targeting the PI3K/AKT/mTOR Pathway for Breast Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Endometrial Cancer 7:00 PM – 8:30 PM CT (8:00 PM – 9:30 PM ET)
	CAR T-Cell Therapy and Bispecific Antibodies for Non-Hodgkin Lymphoma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Monday June 1	ADCs for Breast Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Novel Therapies for Non-Hodgkin Lymphoma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Relapsed/Refractory Multiple Myeloma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Tuesday June 2	Myelofibrosis (Webinar)

Consensus or Controversy? Documenting and Discussing Investigators' Approaches to the Use of Oral SERDs and Agents Targeting the PI3K/AKT/mTOR Pathway in Breast Cancer

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Joyce O'Shaughnessy, MD

Nicholas Turner, MD, PhD

Moderator

Sara M Tolaney, MD, MPH

Agenda

Module 1: Current and Future Roles of Agents Targeting the PI3K/AKT/mTOR Pathway and Oral SERDs in First-Line Therapy for HR-Positive, HER2-Negative Metastatic Breast Cancer (mBC) — Dr Turner

Module 2: Role of Oral SERD Monotherapy in the Treatment of Progressive HR-Positive, HER2-Negative mBC — Dr O'Shaughnessy

Module 3: Potential Use of Oral SERD-Containing Combination Regimens in Managing Progressive HR-Positive, HER2-Negative mBC — Dr Mayer

Module 4: Clinical Utility of Agents Targeting the PI3K/AKT/mTOR Pathway for Patients with Progressive HR-Positive, HER2-Negative mBC — Dr Hurvitz

Module 5: Potential Use of Oral SERDs for HR-Positive, HER2-Negative Localized BC — Dr Tolaney

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Module 5: Potential Use of Oral SERDs for HR-Positive, HER2-Negative Localized BC — Dr Tolaney

Current and Future Role of Agents Targeting the PI3K/AKT/mTOR Pathway and Oral Selective Estrogen Receptor Degraders (SERDs) in First-Line Therapy for Hormone Receptor (HR)-Positive, HER2-Negative Metastatic Breast Cancer (mBC)

Nicholas Turner



The Royal Marsden
NHS Foundation Trust

ICR The Institute of
Cancer Research

First-Line Therapy for HR+/HER2- Metastatic Breast Cancer

- First-line therapy for patients
 - Relapsing on endocrine therapy
 - AI sensitive (endocrine naïve or >12 months break from adjuvant ET)
- Current clinical trials
- Biomarker testing in and after the first-line setting

Fulvestrant plus CDK4/6i studies

MONALEESA-3

HR=0.59; delta 7.7 months¹

PFS

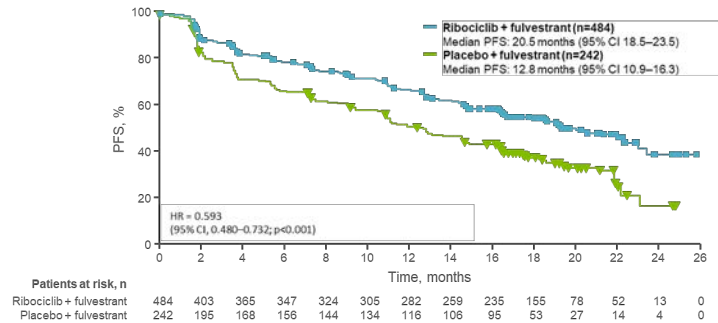


Figure adapted from Slamon, et al. 2018.¹

MONARCH-2

HR=0.55; delta 7 months²

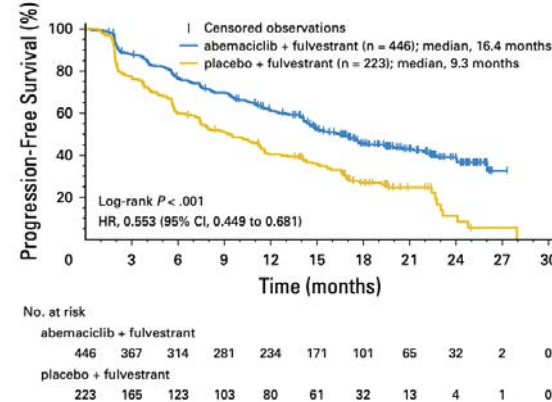


Figure adapted from Sledge GW et al. 2017.²

PALOMA-3

HR=0.46; delta 4.9 months³

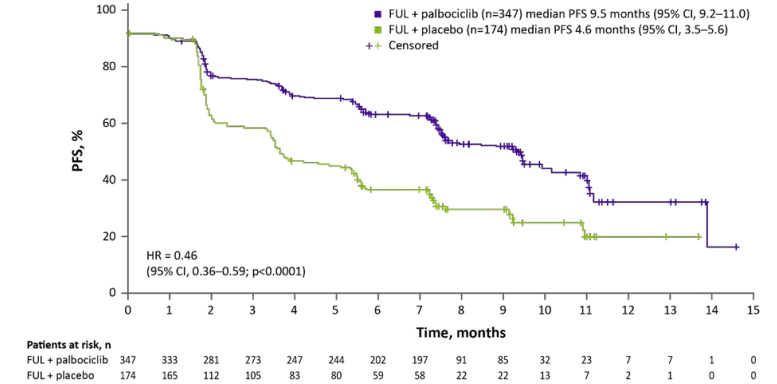
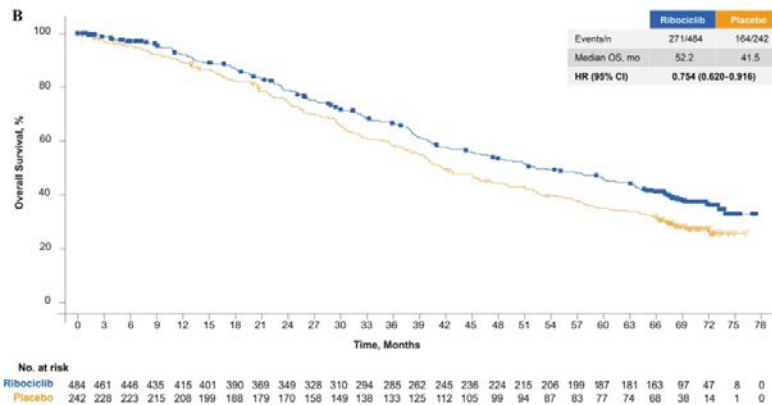


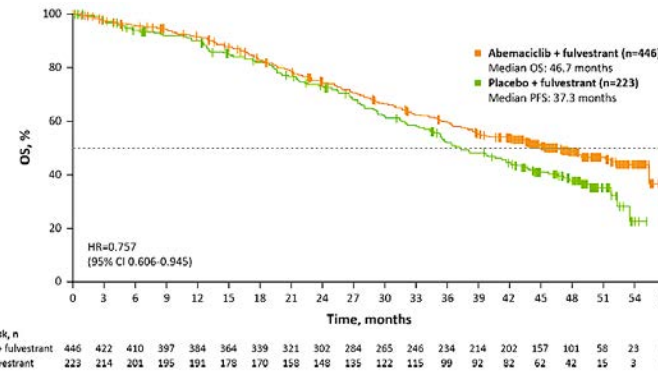
Figure adapted from Cristofanilli M et al. 2016.³

HR=0.75⁴

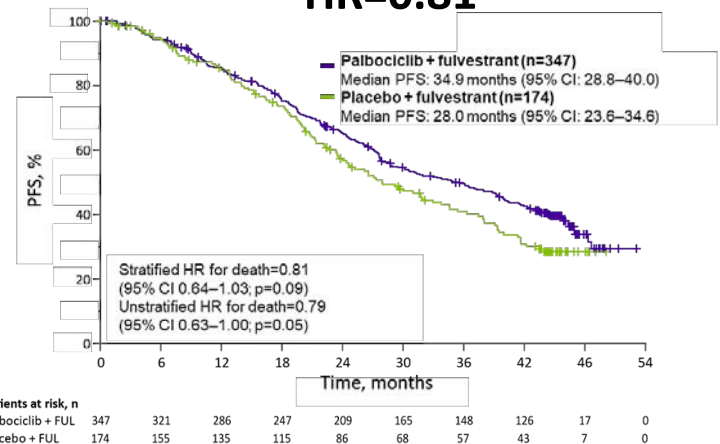
OS



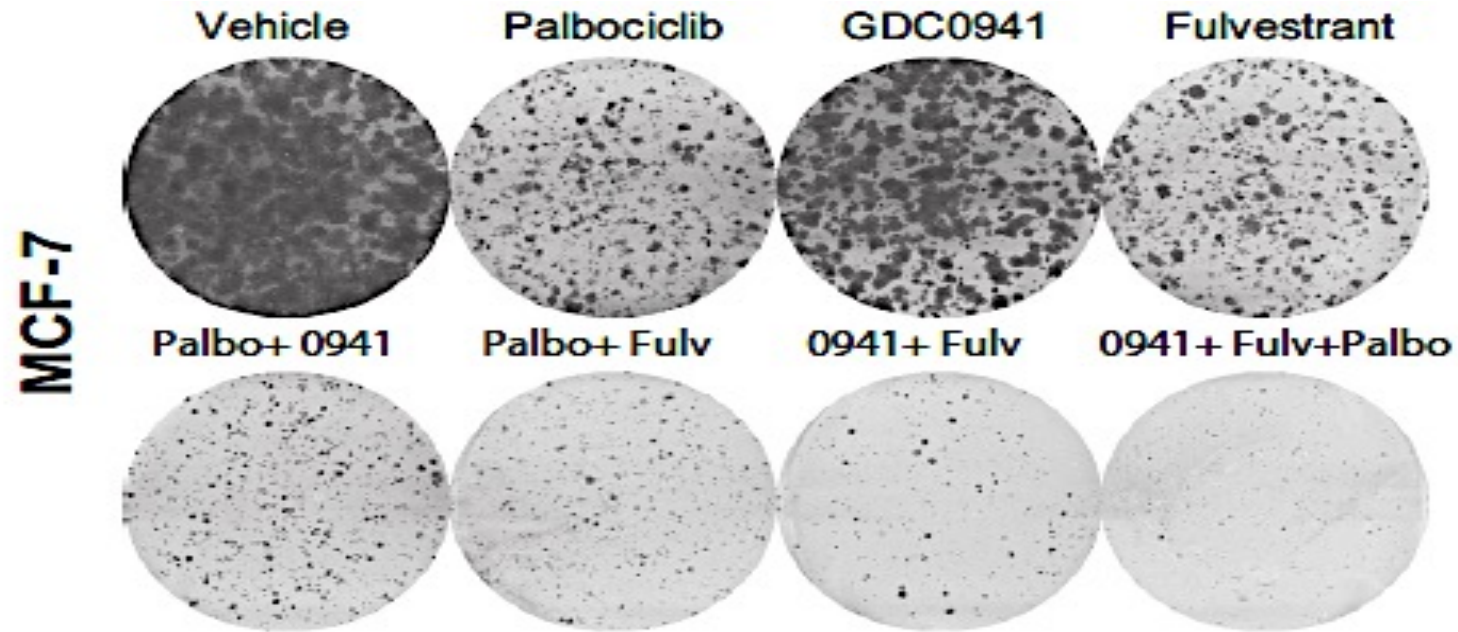
HR=0.76⁵



HR=0.81⁶



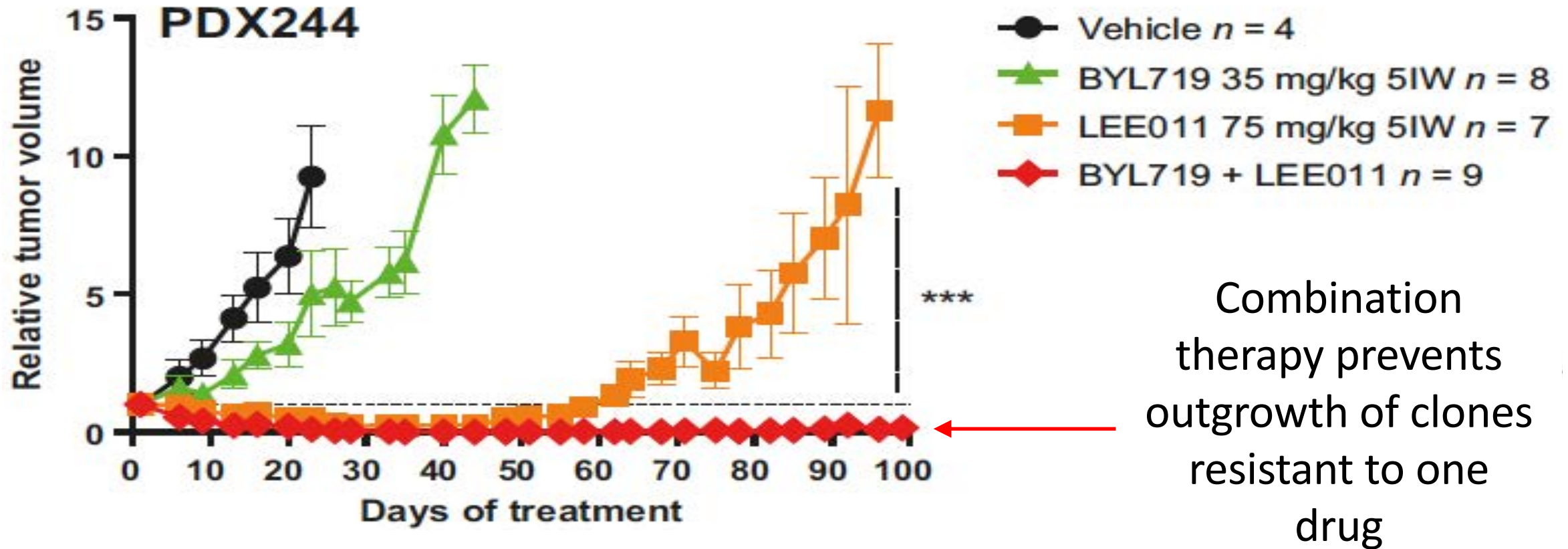
Triplet therapy superior to doublet therapy *in vitro*



Targeting the three fundamental aspects of ER positive breast cancer biology

Oestrogen receptor signalling
CDK4/6 cell cycle entry
PI3 kinase mitogenic signalling

Combination therapy prevents acquired resistance



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%

Stratification factors:

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

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

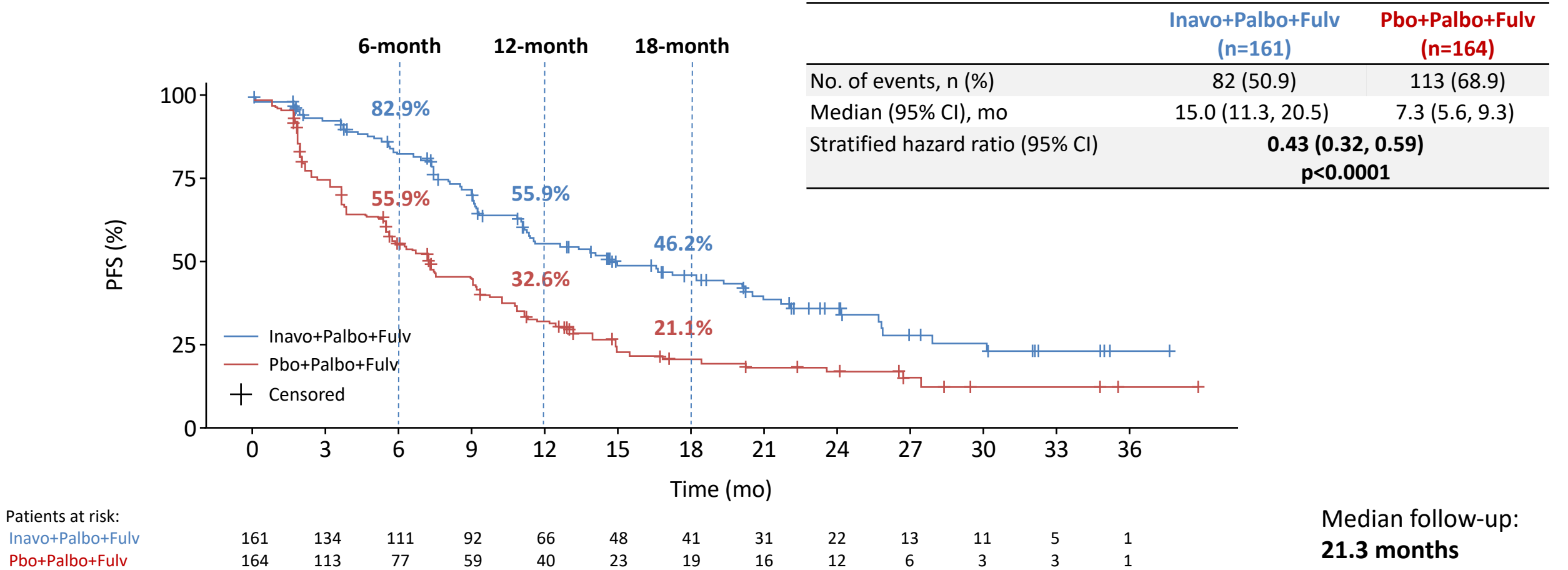
Endpoints

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

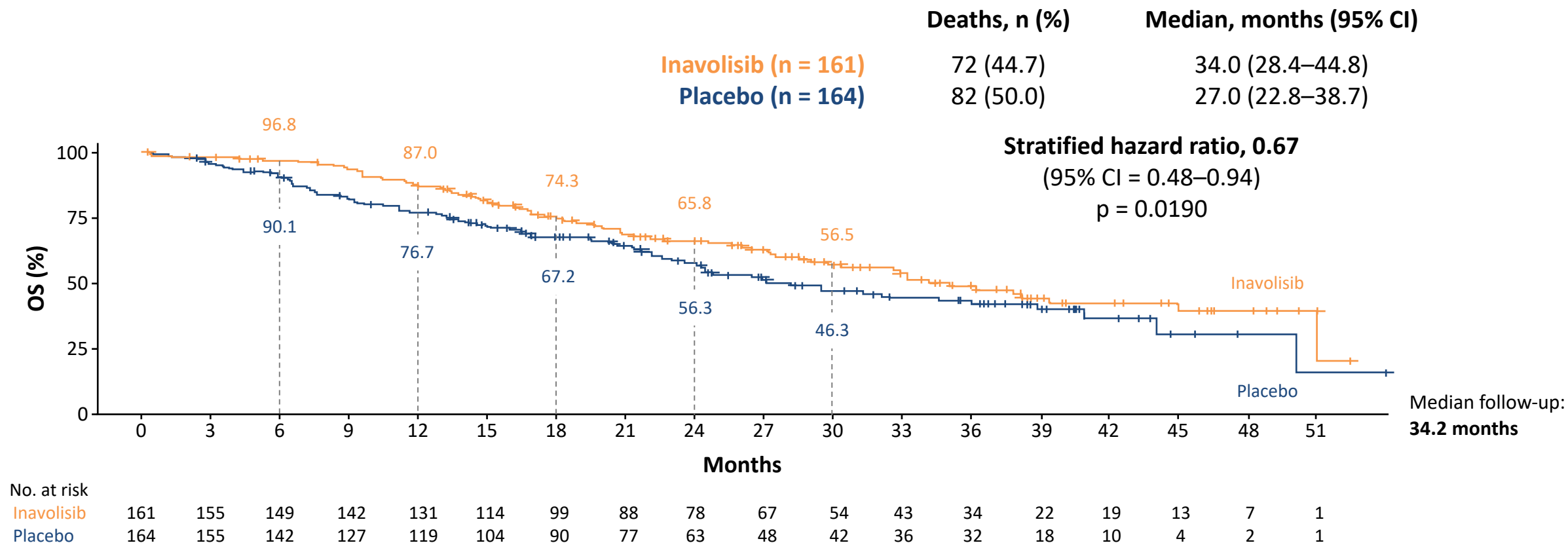
Inavolisib: alpha selective PI3 kinase inhibitor, selectively degrades mutant *PIK3CA*

All drugs in triplet given at maximum single agent doses in the triplet

Primary endpoint: PFS (investigator-assessed)

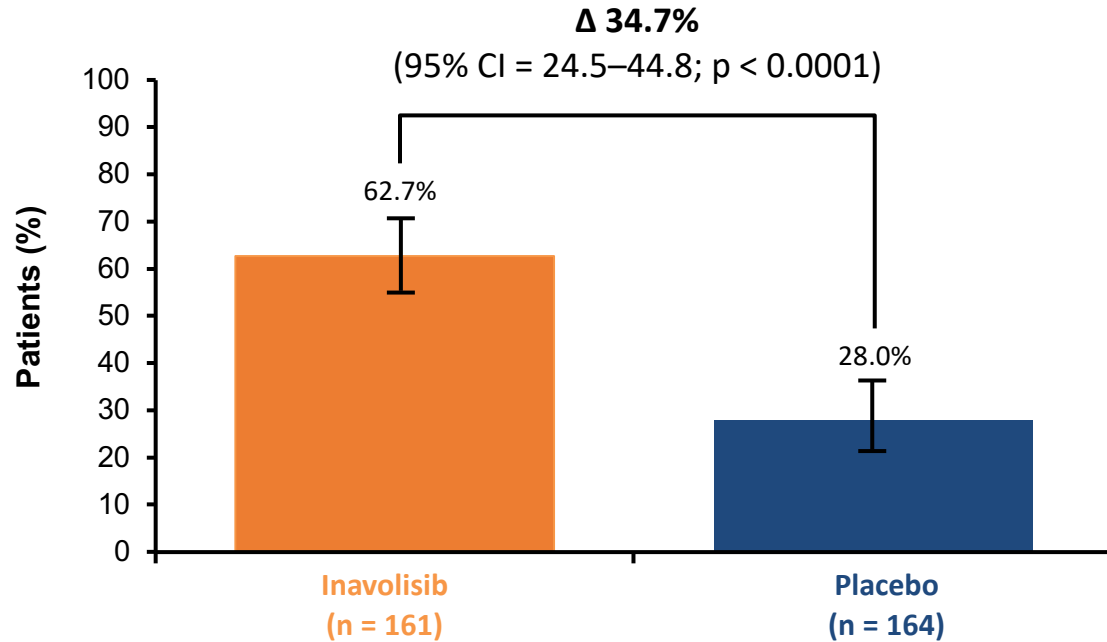


INAVO120 key secondary endpoint: OS

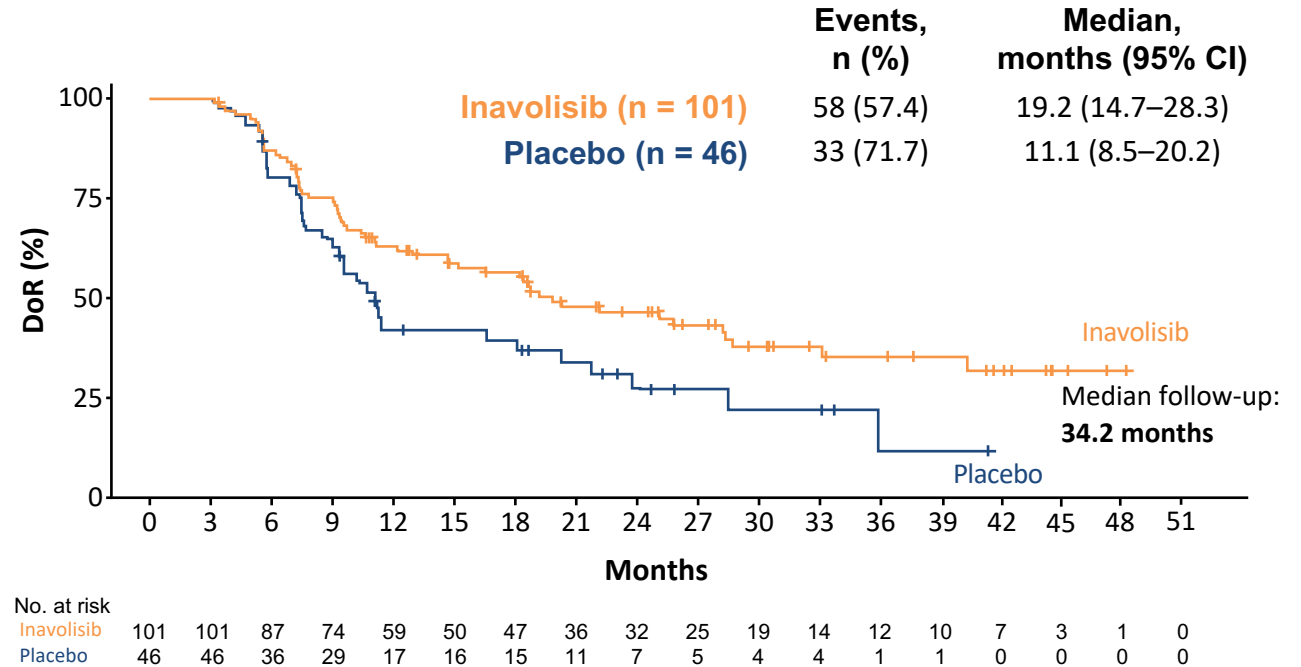


INAVO120 other key secondary endpoints

ORR*



DoR



Clinical confirmation that the triplet delayed acquired resistance

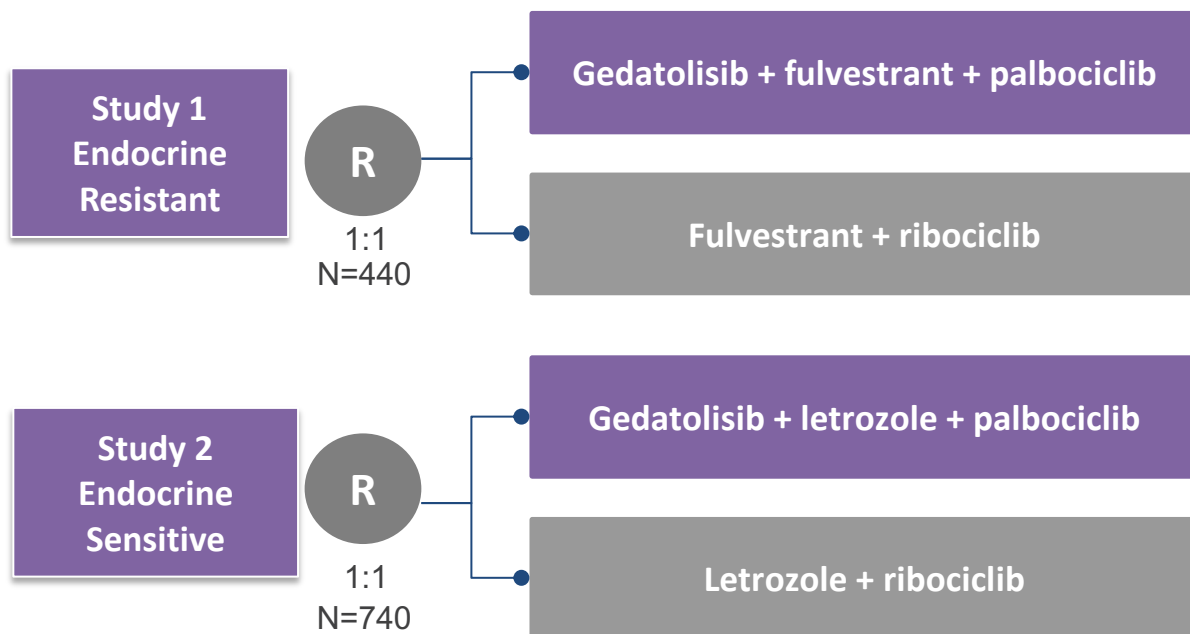
INAVO120 adverse effects

	Inavolisib (n = 161)		Placebo (n = 163)	
Patients, n (%)	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Neutropenia	147 (91.3)	133 (82.6)	148 (90.8)	131 (80.4)
Thrombocytopenia	80 (49.7)	22 (13.7)	75 (46.0)	8 (4.9)
Stomatitis or mucosal inflammation	89 (55.3)	9 (5.6)	47 (28.8)	0
Anemia	64 (39.8)	11 (6.8)	62 (38.0)	3 (1.8)
Hyperglycemia	102 (63.4)	11 (6.8)	22 (13.5)	0
Diarrhea[†]	84 (52.2)	6 (3.7)	26 (16.0)	0
Nausea	47 (29.2)	0	32 (19.6)	0
Rash	43 (26.7)	0	32 (19.6)	1 (0.6)
Ocular toxicities[‡]	47 (29.2)	1 (0.6)	26 (16.0)	0
Aspartate transaminase/ alanine transaminase increase	34 (21.1)	7 (4.3)	37 (22.7)	4 (2.5)
Vomiting	26 (16.1)	2 (1.2)	10 (6.1)	2 (1.2)
Lymphopenia	6 (3.7)	1 (0.6)	15 (9.2)	3 (1.8)
Pneumonitis [§]	5 (3.1)	1 (0.6)	2 (1.2)	0

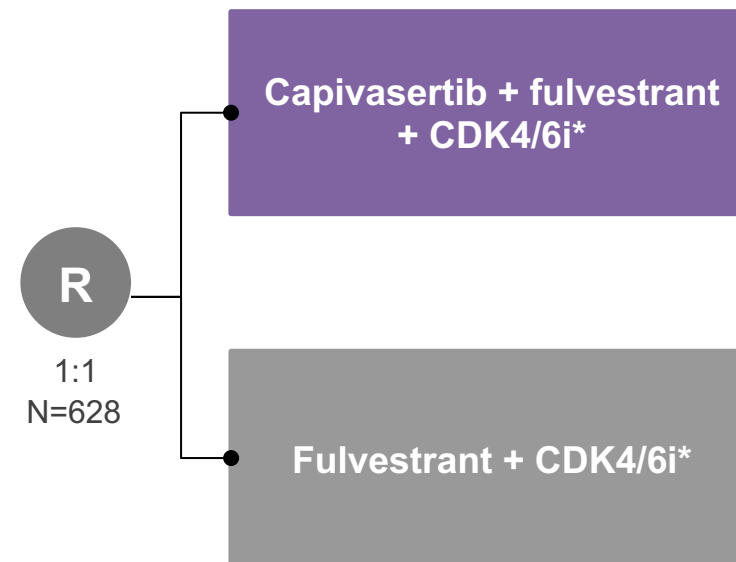
Ongoing 1L trials relapsing on endocrine therapy

1st line triplet studies – not biomarker selected

VIKTORIA-2



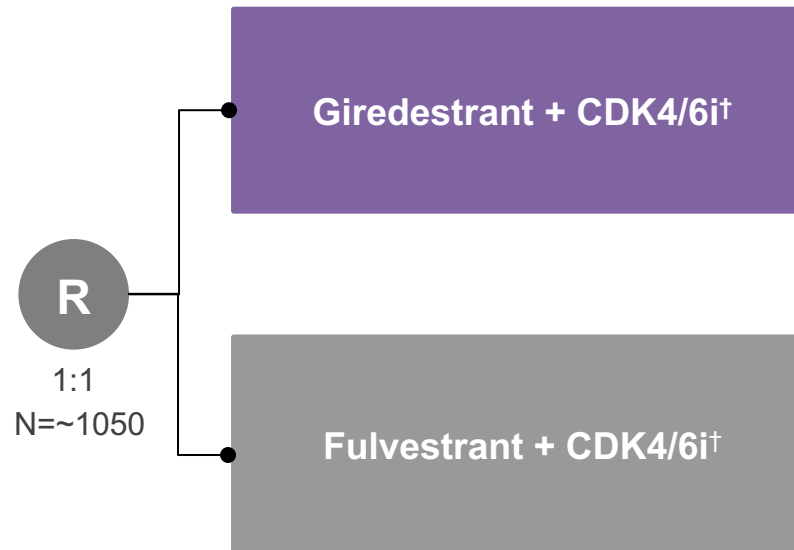
CAPItello-292



pionERA

Eligibility criteria:

- HR-positive, HER2-negative locally advanced or mBC
- Relapse on prior standard adjuvant ET on treatment after ≥ 12 months or off treatment within 12 months of completion (prior adjuvant CDK4/6i allowed)
- Confirmed *ESR1*m status by ctDNA*
- No prior systemic treatment for mBC



Primary:

- PFS investigator *ESR1*m population and overall

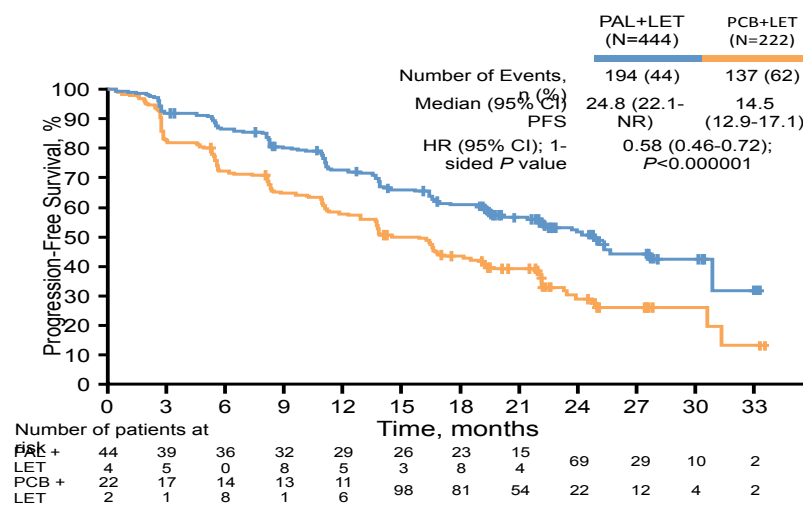
Secondary:

- PFS (*ESR1*wt)
- OS
- cORR, DoR, and CBR

Enriched for *ESR1* mutations (~15% of patients relapsing on AI have *ESR1* mutation at relapse)

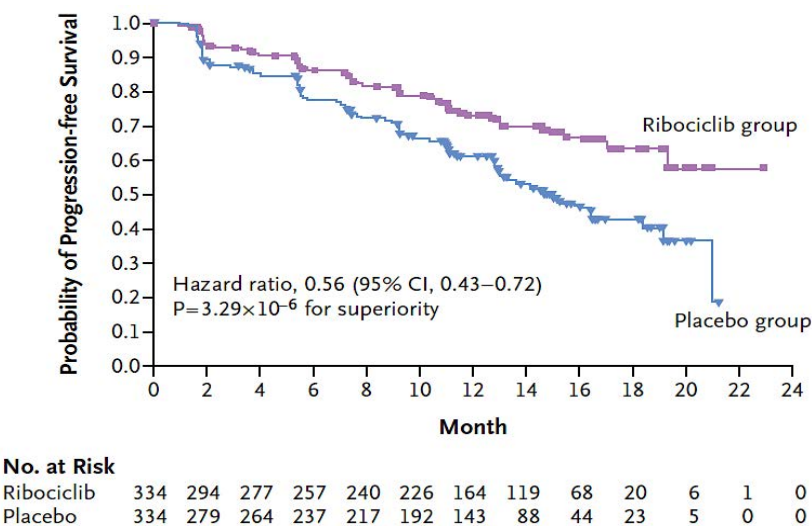
First-line AI sensitive trials with CDK4/6 inhibitors

PALOMA2



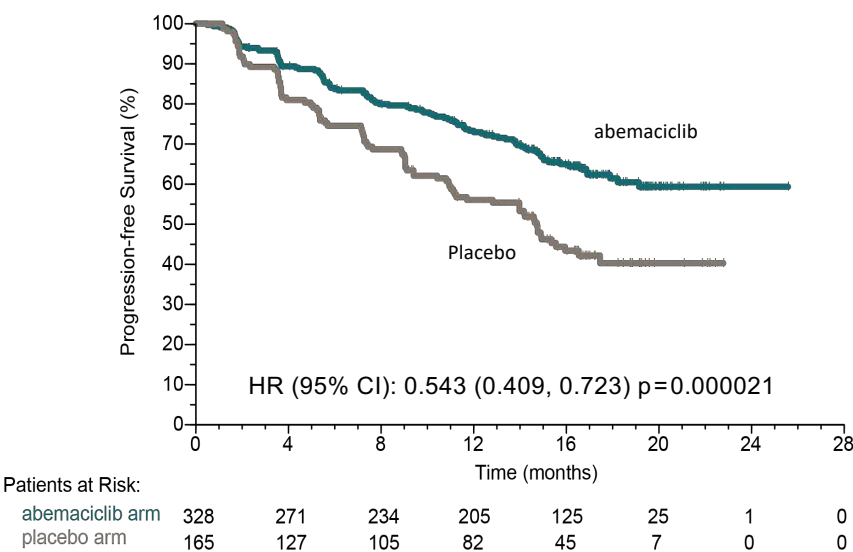
Finn *et al* NEJM 2016

MONALEESA2



Hortobagyi *et al* NEJM 2016

MONARCH3



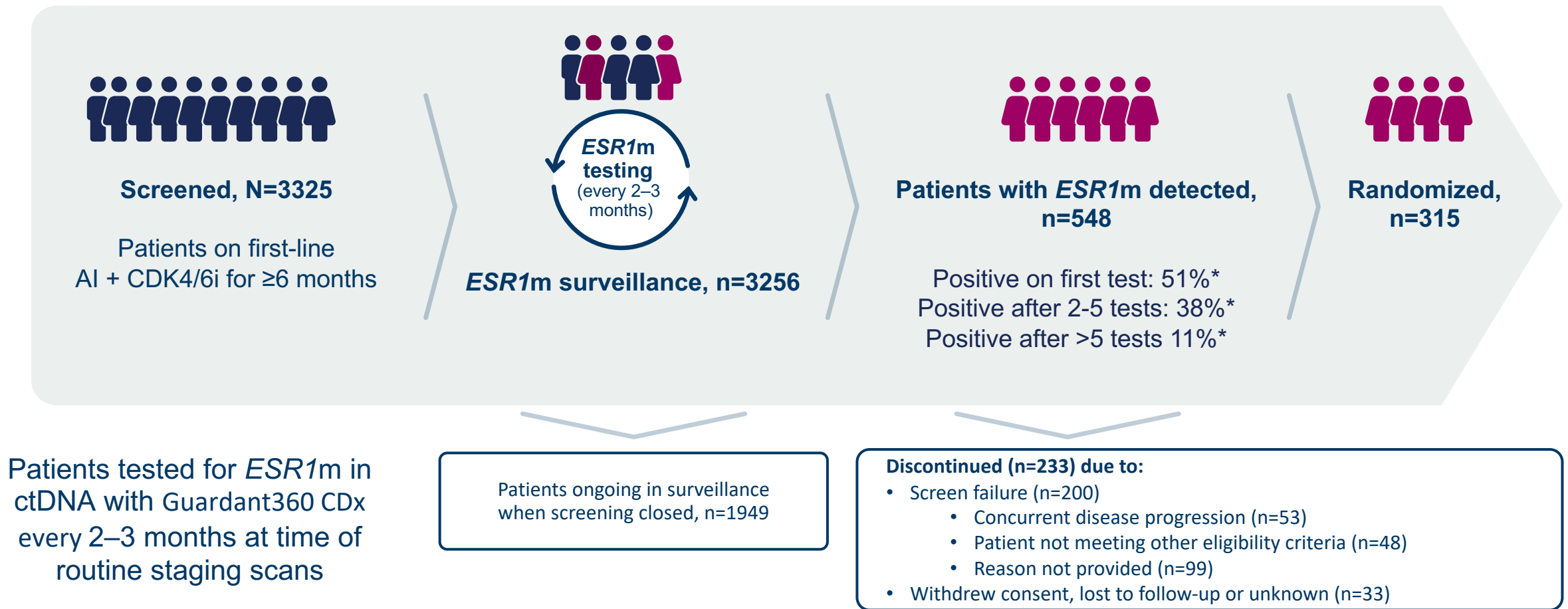
Di Leo *et al* JCO 2017

Camizestrant + CDK4/6 inhibitor for the treatment of emergent *ESR1* mutations during first-line endocrine-based therapy and ahead of disease progression in patients with HR+/HER2– advanced breast cancer: Phase 3, double-blind ctDNA-guided SERENA-6 trial

Nicholas Turner

Royal Marsden Hospital, London, UK

SERENA-6 trial



An estimate of the proportion of patients with emerging *ESR1m* during the study period is 42%, calculated from the 548 patients with a positive test/(the number of patients tested for *ESR1m* [n=3256] minus the number of patients that were still ongoing in surveillance when screening closed [n=1949]).

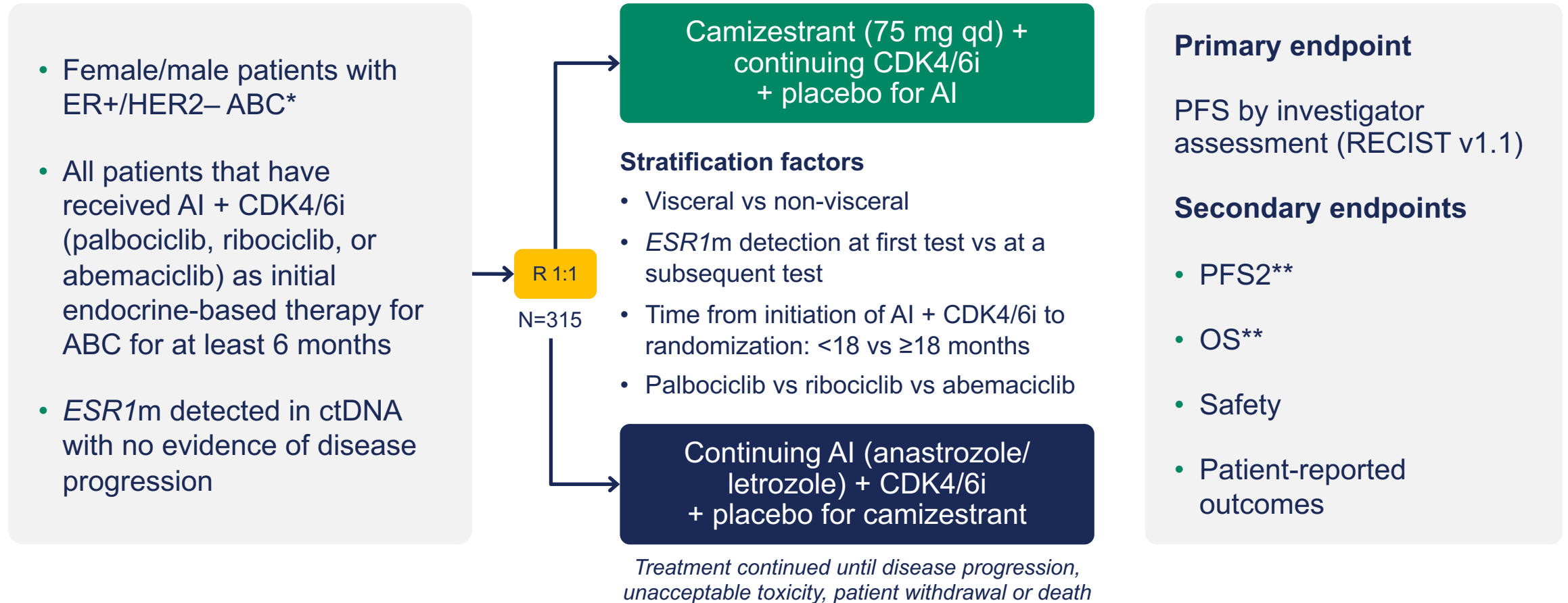
Number of tests to obtain a positive *ESR1m* test result based on n=521 patients who met all the eligibility criteria for the *ESR1m* surveillance step.

Patients were screened for inclusion into the study from 264 sites in 23 countries.

Of the 3325 patients screened for inclusion, ctDNA from patient blood samples were tested for *ESR1m* using Guardant360CDx (Guardant Health, Redwood City, CA, US).

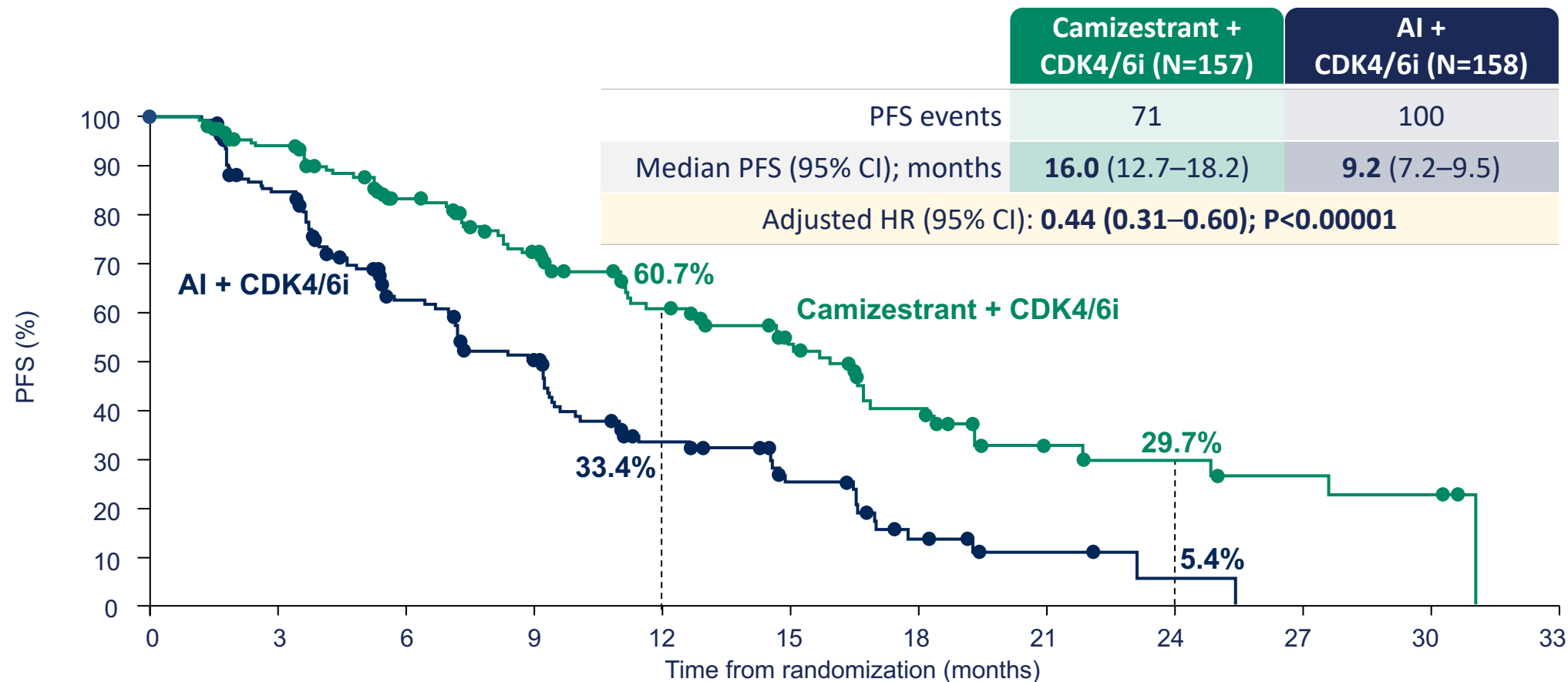
SERENA-6 study design

Phase III, randomized, double-blind, placebo-controlled study (NCT04964934)



*Pre- or perimenopausal women, and men received a luteinizing hormone–releasing hormone agonist per clinical guidelines. **Key secondary endpoint. OS, overall survival; PFS2, second progression-free survival; qd, once daily dose; R, randomized; RECIST, response evaluation criteria in solid tumors.

Primary endpoint: Investigator-assessed PFS

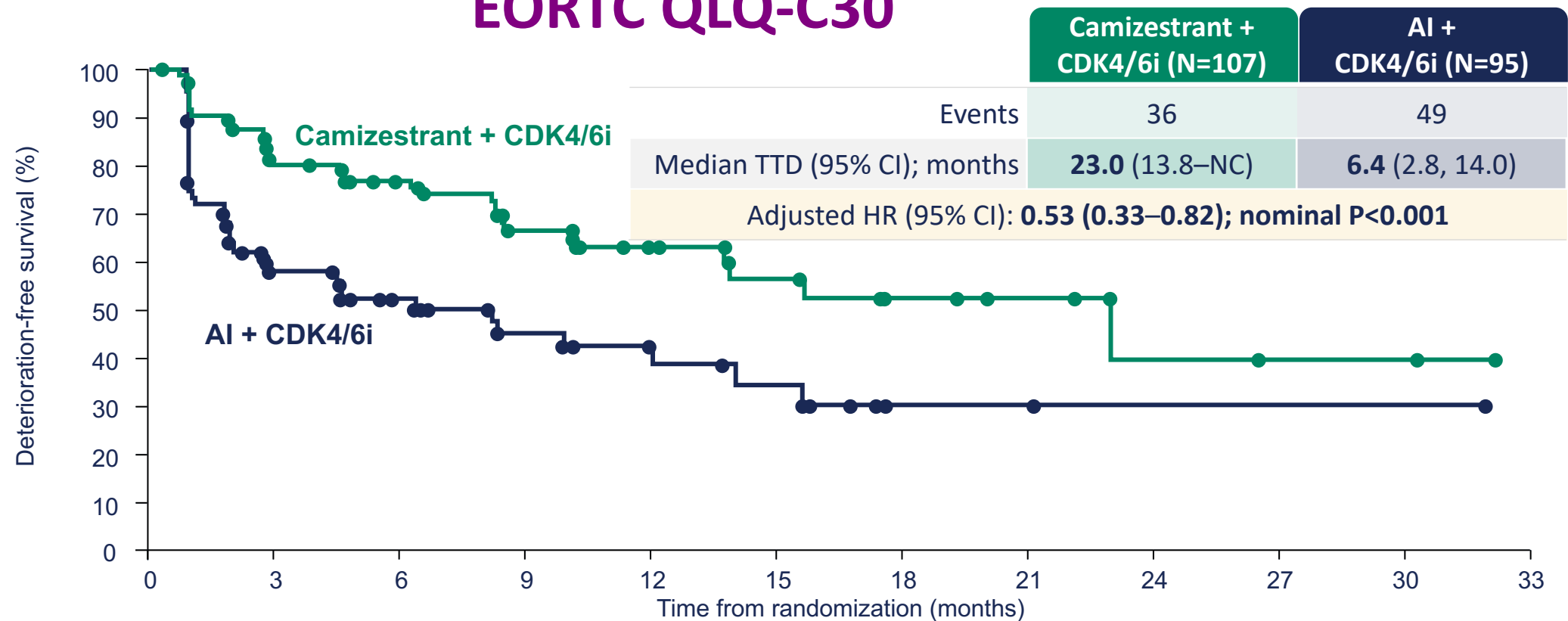


Number of patients at risk												
Camizestrant + CDK4/6i	157	138	105	82	55	41	26	11	9	7	6	0
AI + CDK4/6i	158	124	73	55	29	17	7	3	1	0	0	0

P-value crossed the threshold for significance (P=0.0001). PFS was defined per RECIST v1.1. HR was estimated using the Cox proportional hazard model adjusted for stratification factors.
CI, confidence interval; HR, hazard ratio.

Time to deterioration in global health status/quality of life

EORTC QLQ-C30



Number of patients at risk

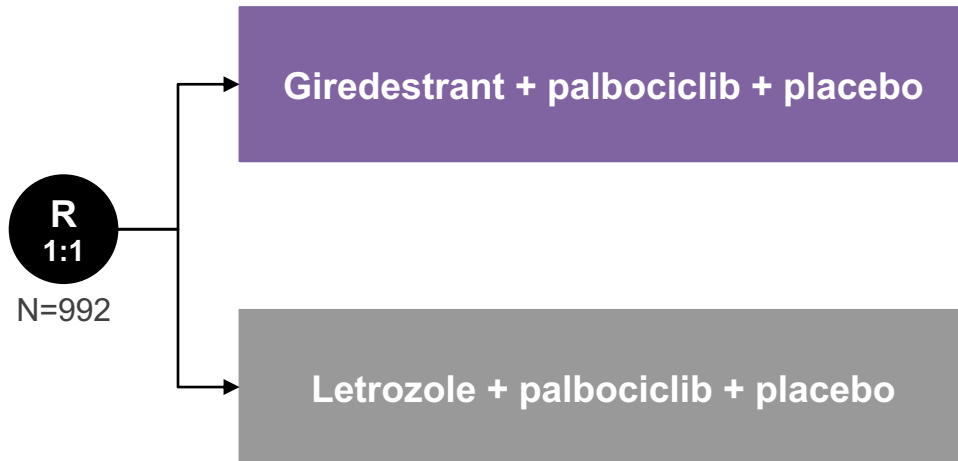
Camizestrant + CDK4/6i	107	72	59	40	24	16	9	6	3	2	2	0
AI + CDK4/6i	95	42	26	16	11	8	2	2	1	1	1	0

- Camizestrant + CDK4/6i also delayed the time to deterioration in pain compared with AI + CDK4/6i

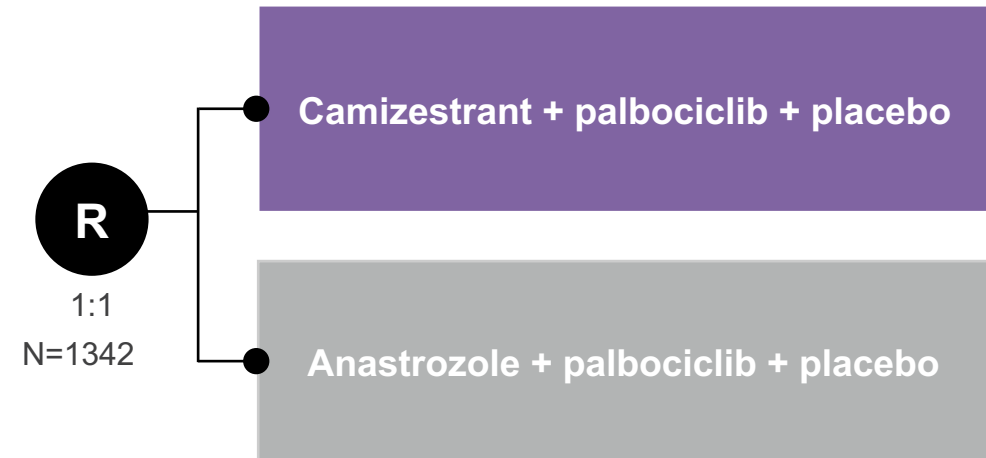
Assessments were conducted at baseline, weeks 4, 8 and 12 and then every 8 weeks until PFS2. Analysis conducted in patients with a baseline score and at least one post-baseline assessment. TTD in global health status/quality of life, an exploratory endpoint, was defined as the time from randomization to first deterioration that was confirmed at a subsequent timepoint measured using the European Organization for Research and Treatment of Cancer 30-item quality-of-life questionnaire (EORTC QLQ-30). Deterioration was defined as a decrease from baseline ≥ 16.6 . HR was estimated using the Cox proportional hazard model stratified by time of *ESR1*m detection (one test vs more than one test), and time from initiation of AI + CDK4/6i to randomization (<18 months vs. ≥ 18 months). NC, not calculable; TTD, time-to-deterioration.

First-line SERD trials

persevERA

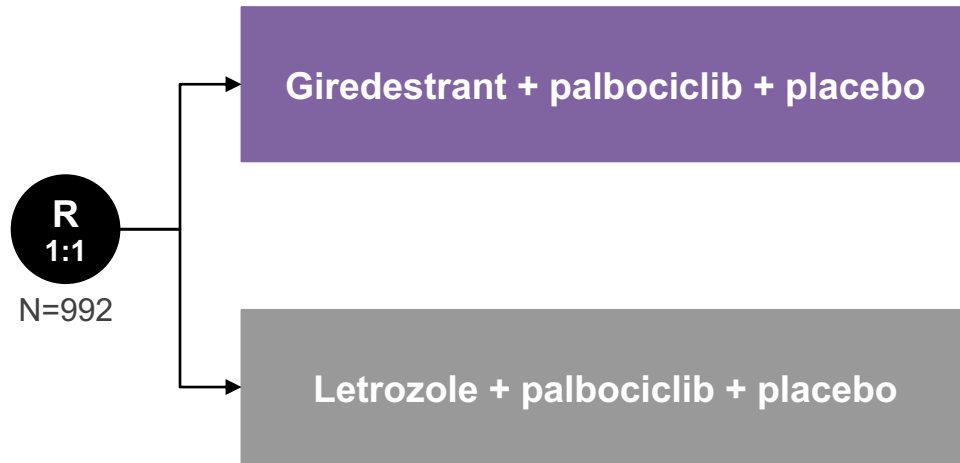


SERENA-4

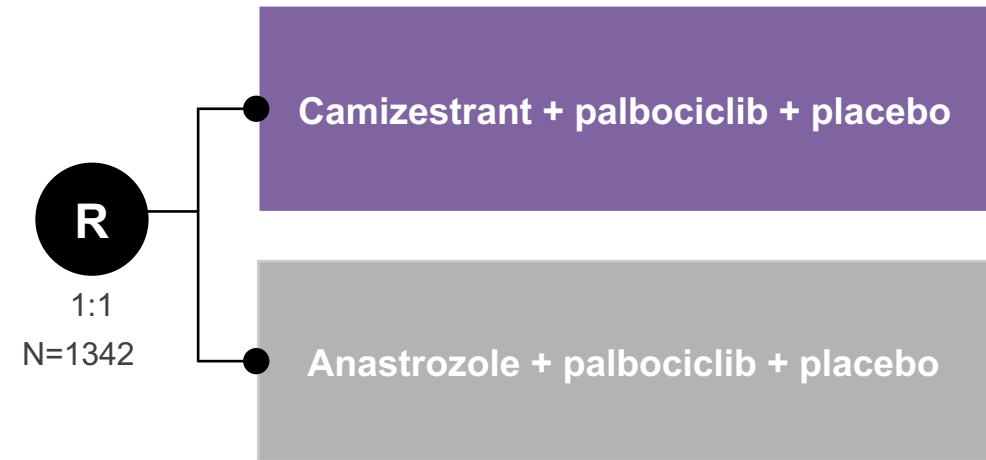


First-line SERD trials

persevERA



SERENA-4



Press release: This study did not meet the primary objective of a statistically significant improvement in PFS, but a numerical improvement was observed.

Results on Tuesday!

Moving oral SERD into the first line setting the best option with *ESR1* surveillance?

Other first-line trials – AI sensitive

Trial	Investigational agent	Randomisation
OPERA-02	Complete Estrogen Receptor Antagonists	Palazestrant + ribociclib vs. letrozole + ribociclib
EvoPAR-BR01	PARP1 inhibitor in <i>BRCA1/2</i> mutant	Saruparib + camizestrant vs. CDK4/6i + ET or camizestrant
FourLight-3	Selective CDK4 inhibitor	Atirmociclib + letrozole vs. CDK4/6i + letrozole
INAVO123	Inavolisib	Inavolisib + CDK4/6i + letrozole vs. CDK4/6i + letrozole

Biomarker testing in metastatic breast cancer

Relapsing on ET

At
Relapse

Fulvestrant + CDK4/6i
+/- inavolisib

At
Progression

Somatic tissue biopsy *PIK3CA/AKT1/PTEN*
?liquid biopsy *PIK3CA*

Somatic liquid biopsy
ESR1/PIK3CA/AKT1/PTEN

Germline testing *BRCA1/BRCA2/PALB2*

Biomarker testing first-line

Relapsing on ET

At
Relapse

Fulvestrant + CDK4/6i
+/- inavolisib

At
Progression

Somatic tissue biopsy *PIK3CA/AKT1/PTEN*
?liquid biopsy PIK3CA

Somatic liquid biopsy
ESR1/PIK3CA/AKT1/PTEN

AI sensitive

At
Relapse

AI + CDK4/6i

At
Progression

Somatic
tissue biopsy *PIK3CA/AKT1/PTEN*

ctDNA *ESR1* monitoring

Somatic liquid biopsy
ESR1/PIK3CA/AKT1/PTEN

Germline testing *BRCA1/BRCA2/PALB2*

At what point do you typically first assess for the following alterations in your patients with HR-positive, HER2-negative breast cancer?

	PIK3CA/AKT1/PTEN	ESR1
 Dr Hurvitz	At diagnosis of metastasis	At diagnosis of metastasis
 Dr Mayer	At diagnosis of metastasis	At diagnosis of metastasis
 Dr O'Shaughnessy	At diagnosis of metastasis	At diagnosis of metastasis
 Dr Tolaney	At diagnosis of metastasis	After disease progression on first-line therapy for metastatic disease
 Dr Turner	At diagnosis of metastasis and after PD on first-line therapy for metastatic disease	After disease progression on first-line therapy for metastatic disease
 Dr Kaklamani	At diagnosis of metastasis	After disease progression on first-line therapy for metastatic disease

PD = disease progression; ctDNA = circulating tumor DNA

Which first-line treatment would you recommend for a 65-year-old woman (PS 0) with ER/PR-positive, HER2-low (IHC 1+) breast cancer who develops metastatic disease after 2 years of a planned 5 years of adjuvant aromatase inhibitor (AI) therapy?

Her biomarker testing results are:

- **PIK3CA-positive**
- **ESR1-negative**
- **BRCA wild type**

Age 65, PS 0; develops metastatic disease after 2 years of a planned 5 years of adjuvant AI therapy

PIK3CA-positive, ESR1-negative, BRCA wild type

	Multiple minimally symptomatic bone metastases	Multiple symptomatic visceral metastases and normal LFTs
 Dr Hurvitz	Inavolisib + palbociclib + fulvestrant	Inavolisib + palbociclib + fulvestrant
 Dr Mayer	Inavolisib + palbociclib + fulvestrant	Inavolisib + palbociclib + fulvestrant
 Dr O'Shaughnessy	Inavolisib + palbociclib + fulvestrant	Inavolisib + palbociclib + fulvestrant
 Dr Tolaney	Inavolisib + palbociclib + fulvestrant	Inavolisib + palbociclib + fulvestrant
 Dr Turner	Inavolisib + palbociclib + fulvestrant	Inavolisib + palbociclib + fulvestrant
 Dr Kaklamani	Inavolisib + palbociclib + fulvestrant	Inavolisib + palbociclib + fulvestrant

LFTs = liver function tests

Which first-line treatment would you recommend for a 65-year-old woman (PS 0) with ER/PR-positive, HER2-low (IHC 1+) breast cancer who develops minimally symptomatic bone metastases after 2 years of a planned 5 years of treatment with adjuvant AI and adjuvant abemaciclib?

Her biomarker testing results are:

- PIK3CA-positive
- ESR1-negative
- BRCA wild type

Age 65, PS 0; minimally symptomatic bone metastases after 2 years of a planned 5 years of treatment with adjuvant AI and adjuvant abemaciclib
PIK3CA-positive, ESR1-negative, BRCA wild type



Dr Hurvitz

Capivasertib/fulvestrant



Dr Mayer

Inavolisib + palbociclib + fulvestrant



Dr O'Shaughnessy

Inavolisib + palbociclib + fulvestrant



Dr Tolaney

Inavolisib + palbociclib + fulvestrant



Dr Turner

Capivasertib/fulvestrant



Dr Kaklamani

Inavolisib + palbociclib + fulvestrant

Would you offer inavolisib/palbociclib/fulvestrant to a patient with de novo PIK3CA-mutated, HR-positive, HER2-negative mBC under any circumstances?



Dr Hurvitz

No



Dr Mayer

No



Dr O'Shaughnessy

No



Dr Tolaney

No



Dr Turner

No



Dr Kaklamani

No

Do you believe that the results from the SERENA-6 study justify the routine use of serial ctDNA monitoring for early detection of ESR1 mutations in patients with HR-positive, HER2-negative mBC receiving first-line therapy? If yes, how often would you conduct ctDNA analysis?



Dr Hurvitz

No



Dr Mayer

Yes; ctDNA analysis 4 times a year for years 1 to 4



Dr O'Shaughnessy

Yes, ctDNA analysis every 3 months



Dr Tolaney

Yes, ctDNA analysis every 2-3 months, but would start at month 12



Dr Turner

Yes, ctDNA analysis every 3 months, starting at 6 months in



Dr Kaklamani

No

Do you believe the results from the SERENA-6 study justify an early change in therapy for patients in whom an ESR1 mutation is identified on ctDNA without radiographic evidence of disease progression?



Dr Hurvitz

No



Dr Mayer

Yes



Dr O'Shaughnessy

Yes



Dr Tolaney

Yes



Dr Turner

Yes



Dr Kaklamani

No

Do you anticipate that camizestrant will receive regulatory approval for use in the manner evaluated in the SERENA-6 study?



Dr Hurvitz

No



Dr Mayer

Yes



Dr O'Shaughnessy

Yes



Dr Tolaney

No



Dr Turner

Yes



Dr Kaklamani

Yes

Agenda

Module 1: Current and Future Roles of Agents Targeting the PI3K/AKT/mTOR Pathway and Oral SERDs in First-Line Therapy for HR-Positive, HER2-Negative Metastatic Breast Cancer (mBC) — Dr Turner

Module 2: Role of Oral SERD Monotherapy in the Treatment of Progressive HR-Positive, HER2-Negative mBC — Dr O'Shaughnessy

Module 3: Potential Use of Oral SERD-Containing Combination Regimens in Managing Progressive HR-Positive, HER2-Negative mBC — Dr Mayer

Module 4: Clinical Utility of Agents Targeting the PI3K/AKT/mTOR Pathway for Patients with Progressive HR-Positive, HER2-Negative mBC — Dr Hurvitz

Module 5: Potential Use of Oral SERDs for HR-Positive, HER2-Negative Localized BC — Dr Tolaney

Role of Oral SERD Monotherapy for Progressive HR-Positive, HER2-Negative MBC

Joyce O'Shaughnessy, MD

Baylor University Medical Center

Texas Oncology

Sarah Cannon Research Institute

Dallas TX

SERD

Selective Estrogen Receptor Degradar

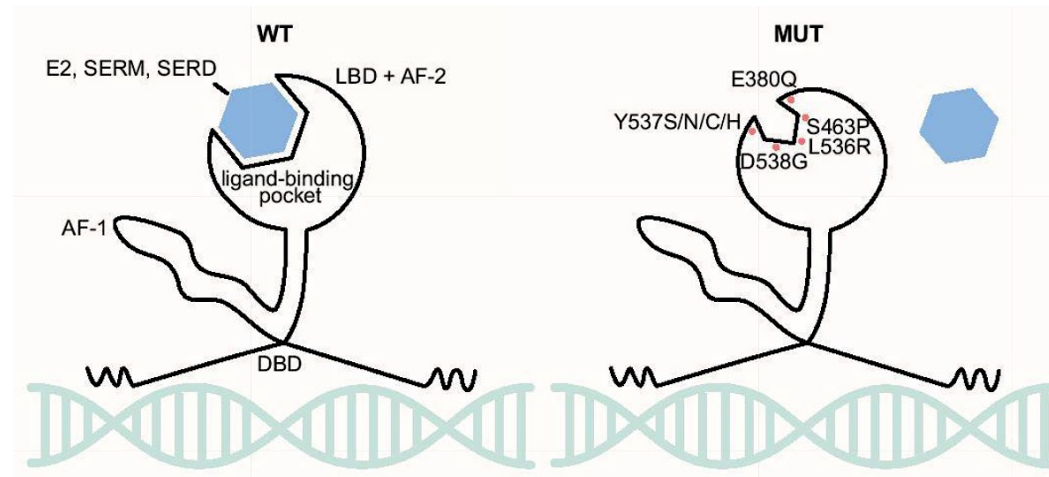
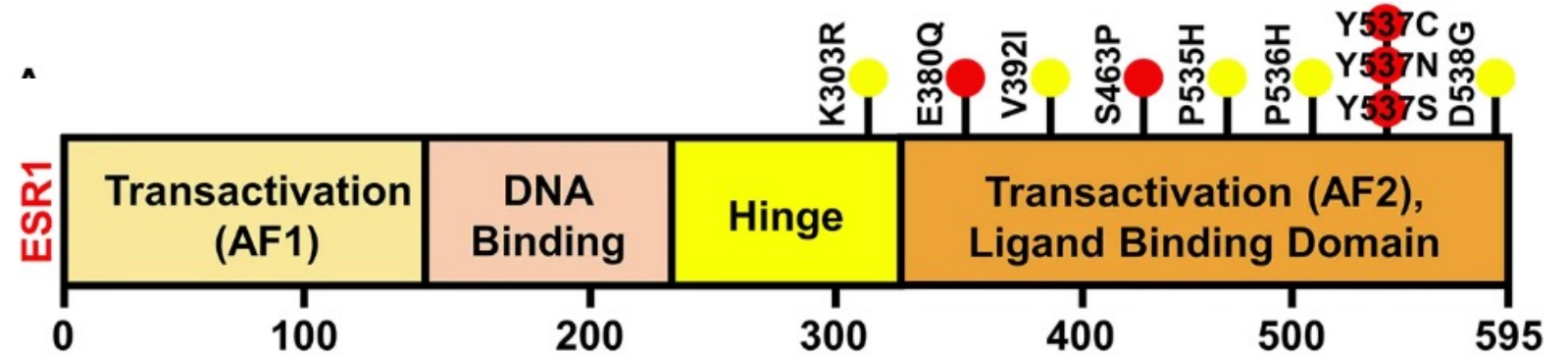
Key advantages

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

ESR1 Gene Mutations and Mechanisms of Resistance

Almost all *ESR1* mutations occur in the ligand binding domain (LBD) coding region and result in constitutively active ER protein

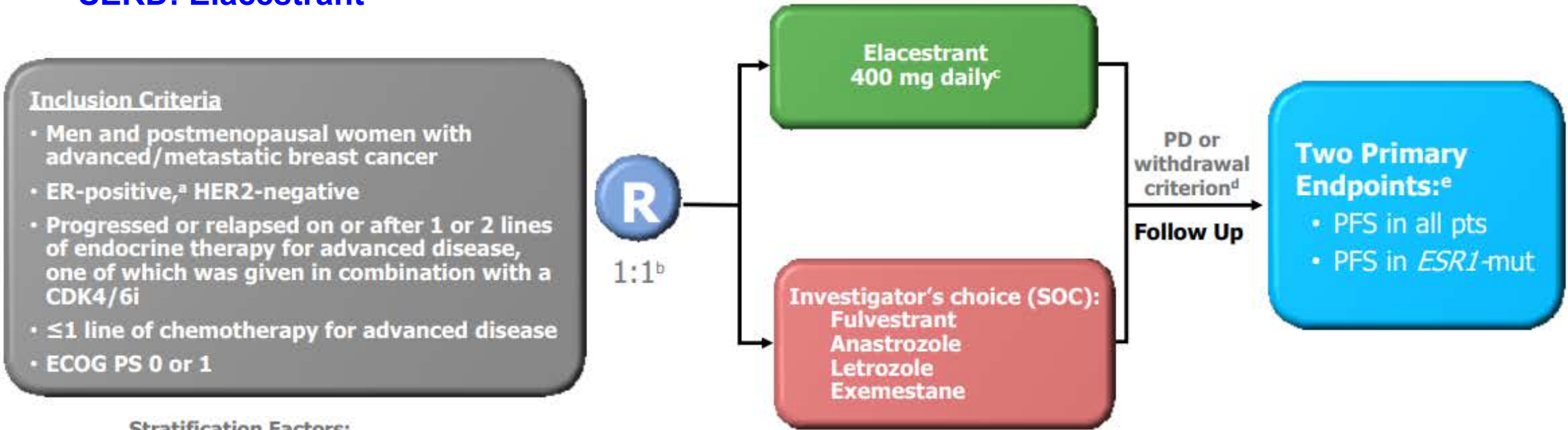
(ie, the ER is always “switched on”)



- | | |
|------------------------------------|-----------------|
| Constitutively active conformation | ↑ Proliferation |
| ↑ Basal transactivator function | ↑ Survival |
| ↓ Affinity for E2, SERM, SERD | ↑ Migration |
| ↑ Proteolytic stability | ↑ AI resistance |

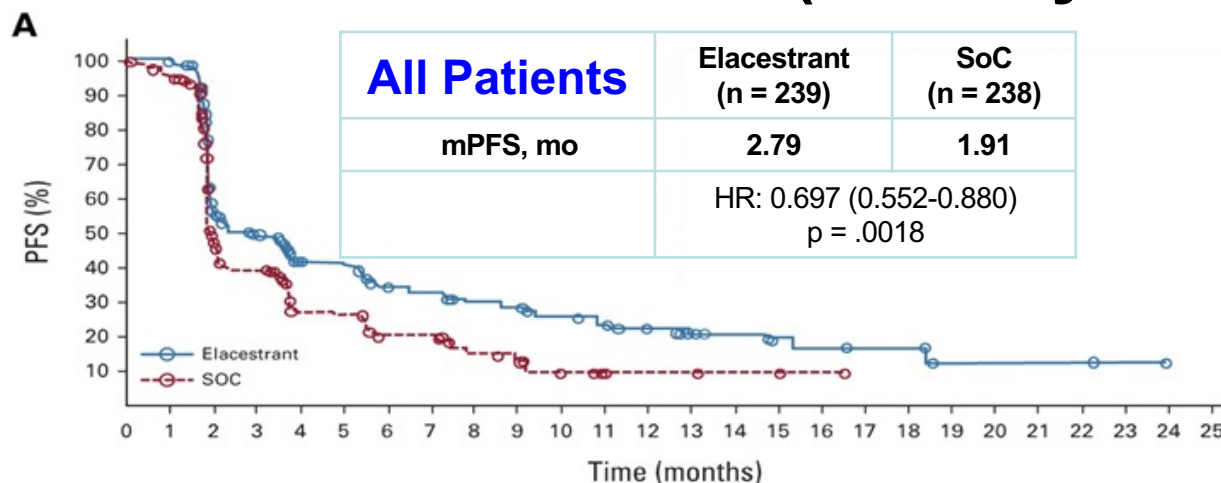
EMERALD: Ph 3 Trial of Elacestrant vs SOC in HR+/HER2- MBC

SERD: Elacestrant

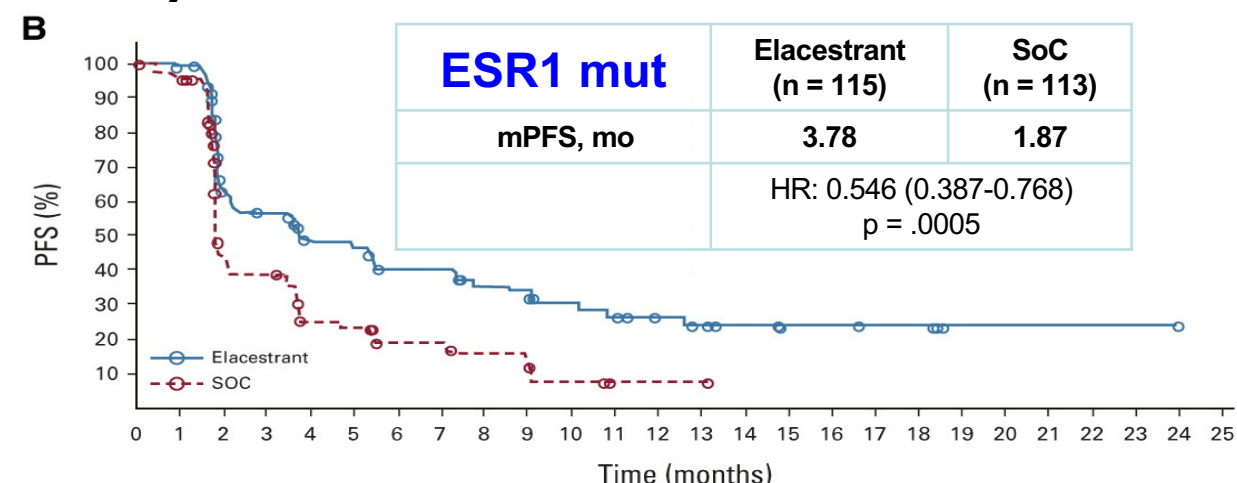


Patient population		
	Elacestrant	SOC
<i>ESR1</i> -mutant	48%	47%
Visceral mets	68%	71%
2 prior lines of ET	46%	41%
Prior chemo	20%	24%
Prior CDK4/6i	100%	100%

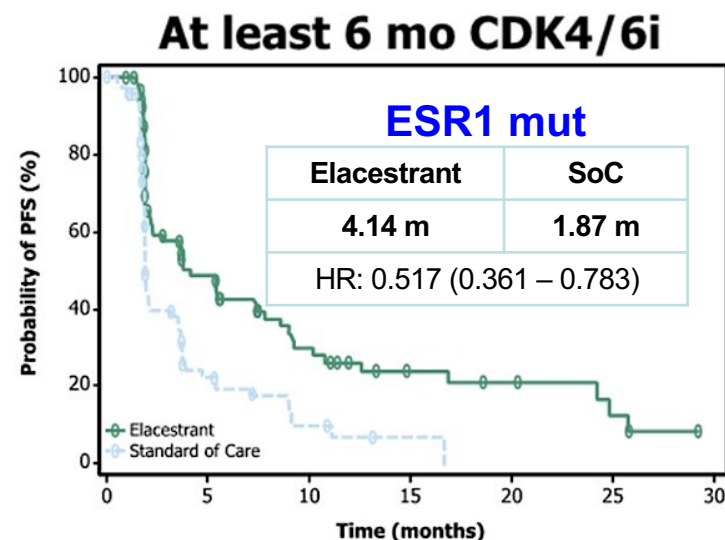
EMERALD: PFS (Primary Endpoint): Elacestrant vs. SOC



No. at risk:																										
Elacestrant	239	223	106	89	60	57	42	40	34	33	27	24	19	13	11	8	7	6	6	2	2	2	2	1	0	
SOC	238	206	84	68	39	38	25	25	16	15	7	4	3	3	2	2	1	0								

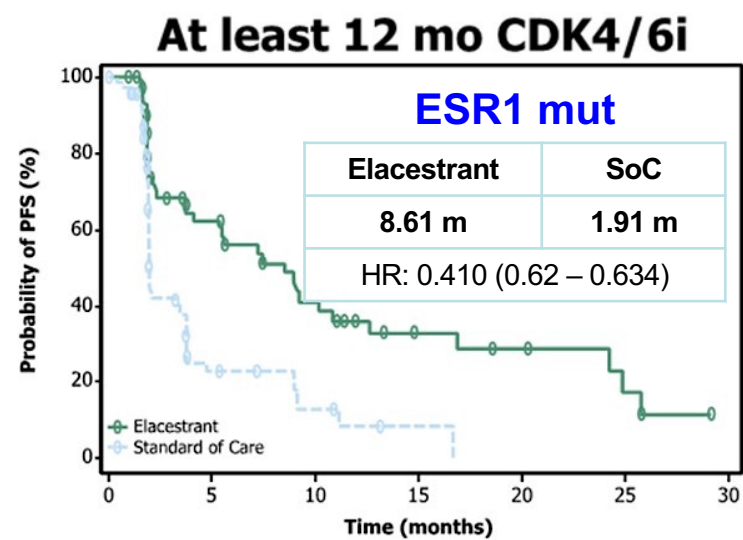


No. at risk:																									
Elacestrant	115	105	54	46	35	33	26	26	21	20	16	14	11	9	7	5	5	4	4	1	1	1	1	1	0
SOC	113	99	39	34	19	18	12	12	9	9	4	1	1	1	0										



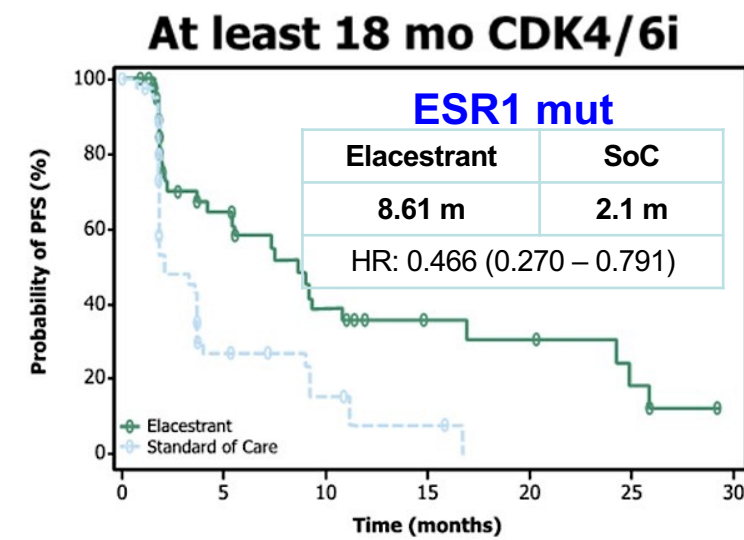
No. at risk:

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Elacestrant	103	50	33	25	20	16	11	9	8	7	6	5	5	1	1	0															
SOC	102	34	16	11	9	5	2	1	1	0																					



No. at risk:

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Elacestrant	78	42	31	24	20	16	11	9	8	7	6	5	5	1	1	0															
SOC	81	26	12	10	9	5	2	1	1	0																					



No. at risk:

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Elacestrant	55	30	23	18	16	12	8	8	7	6	6	5	5	1	1	0															
SOC	56	21	9	8	7	4	1	1	1	0																					

EMERALD Subgroup Analysis: PFS by Subgroup in *ESR1m* Patients With ≥ 12 Months of CDK4/6i

Subgroup	N (%)	Median PFS, mo (95% CI)		HR (95% CI)
		Elacestrant	SoC	
All <i>ESR1m</i>	159 (100)	8.6	1.9	0.41 (0.26-0.63)
<i>ESR1m</i> with liver and/or lung mets	113 (71)	7.3	1.9	0.35 (0.21-0.59)
<i>ESR1m</i> and <i>PIK3CAm</i>	62 (39)	5.5	1.9	0.42 (0.18-0.94)
<i>ESR1m</i> and <i>TP53m</i>	61 (38)	8.6	1.9	0.30 (0.13-0.64)
<i>ESR1m</i> and <i>HER2-low</i>	77 (48)	9.0	1.9	0.30 (0.14-0.60)

Impact of prior treatment, *ESR1* mutational landscape, and co-occurring *PI3K* pathway status on real-world elacestrant outcomes in patients with HER2-advanced breast cancer



Objective

- The study used a large clinical-genomic database to assess the real-world use of elacestrant and examine^a:
 - impact of prior treatments,
 - type/number of *ESR1*-mut, and
 - co-occurring PI3K-pathway alterations on clinical outcomes.



Patients

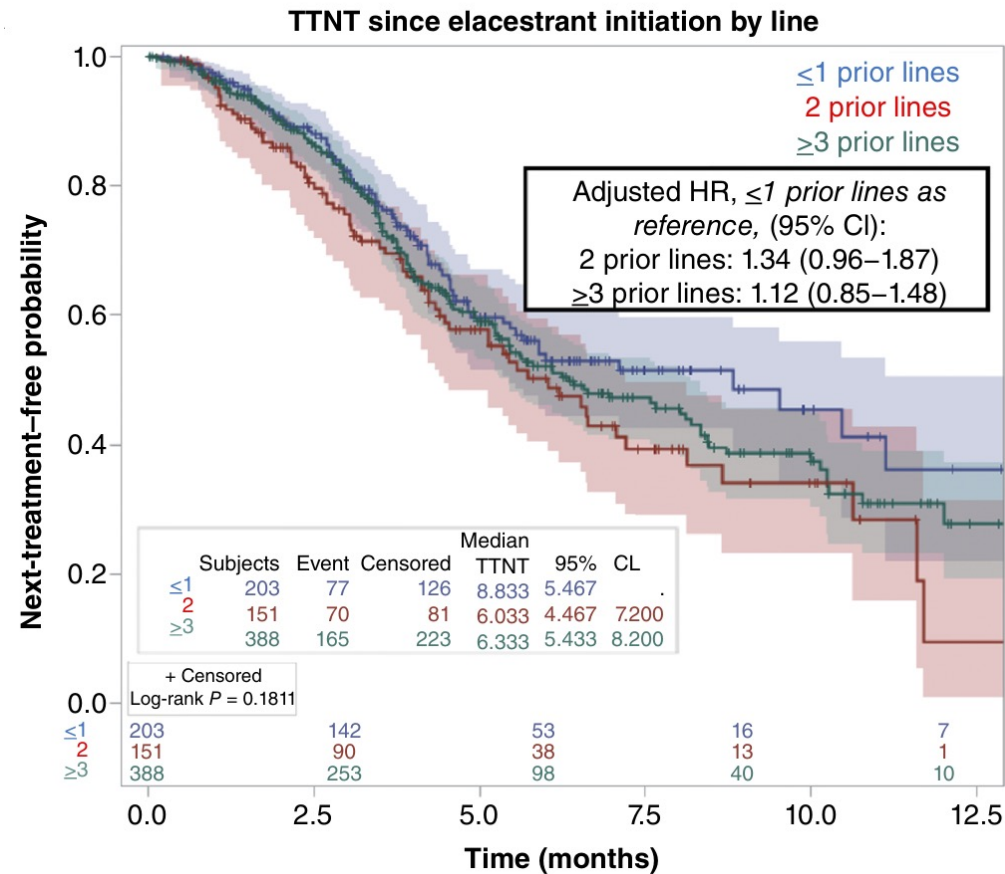
- HR+/HER2-aBC identified via the GuardantINFORM database
- *ESR1*-mut detected on ctDNA within 6 months prior to elacestrant start and treated with elacestrant after FDA approval in January 2023

ctDNA, circulating tumor DNA; HER2-, HER2-negative; HR+, hormone receptor-positive; mut, mutated/mutation; mBC, metastatic breast cancer; PFS, progression-free survival.

^aReal-world time to next treatment was analyzed as a proxy outcome for PFS. Patients were required to have >28 days of follow-up after the first elacestrant claim to be included in outcomes analysis. Non-adjusted Kaplan-Meier curves were generated with 95% CI and Cox-regression hazard ratios adjusted for patient age, gender, year of ctDNA result, and line of therapy were used. Oncogenic alterations in *AKT1*, *PTEN*, and *PIK3CA* with an FDA-approved targeted therapeutic indication were included as PI3K-pathway alterations.

1. Lloyd M et al. SABCS 2024. Poster PS7-05.

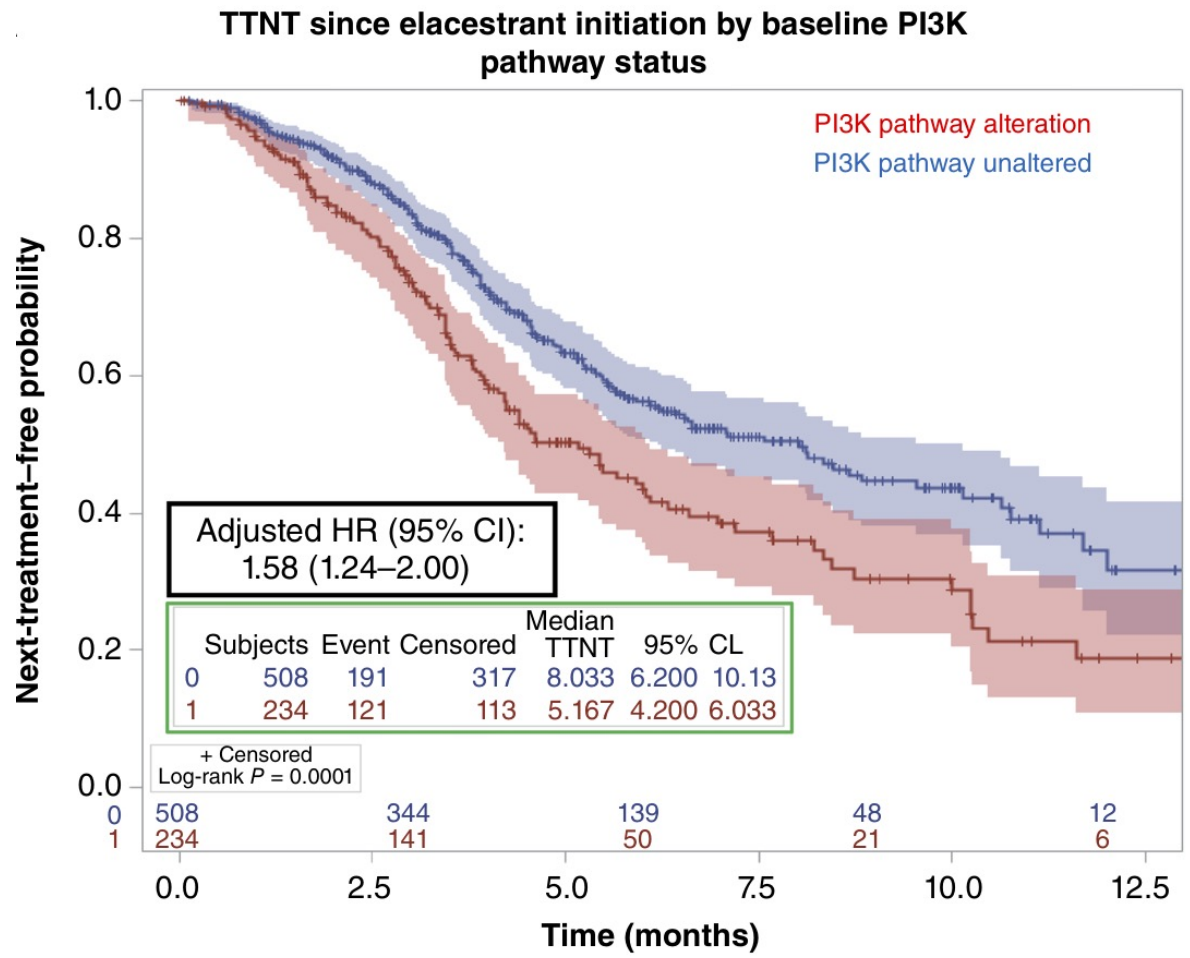
rwTTNT Since Elacestrant Initiation by Line of Treatment



Patient treated in earlier lines (ie, 2L) seemed to have a longer rwTTNT.

Observational retrospective analyses are not intended for direct comparisons with clinical trials.

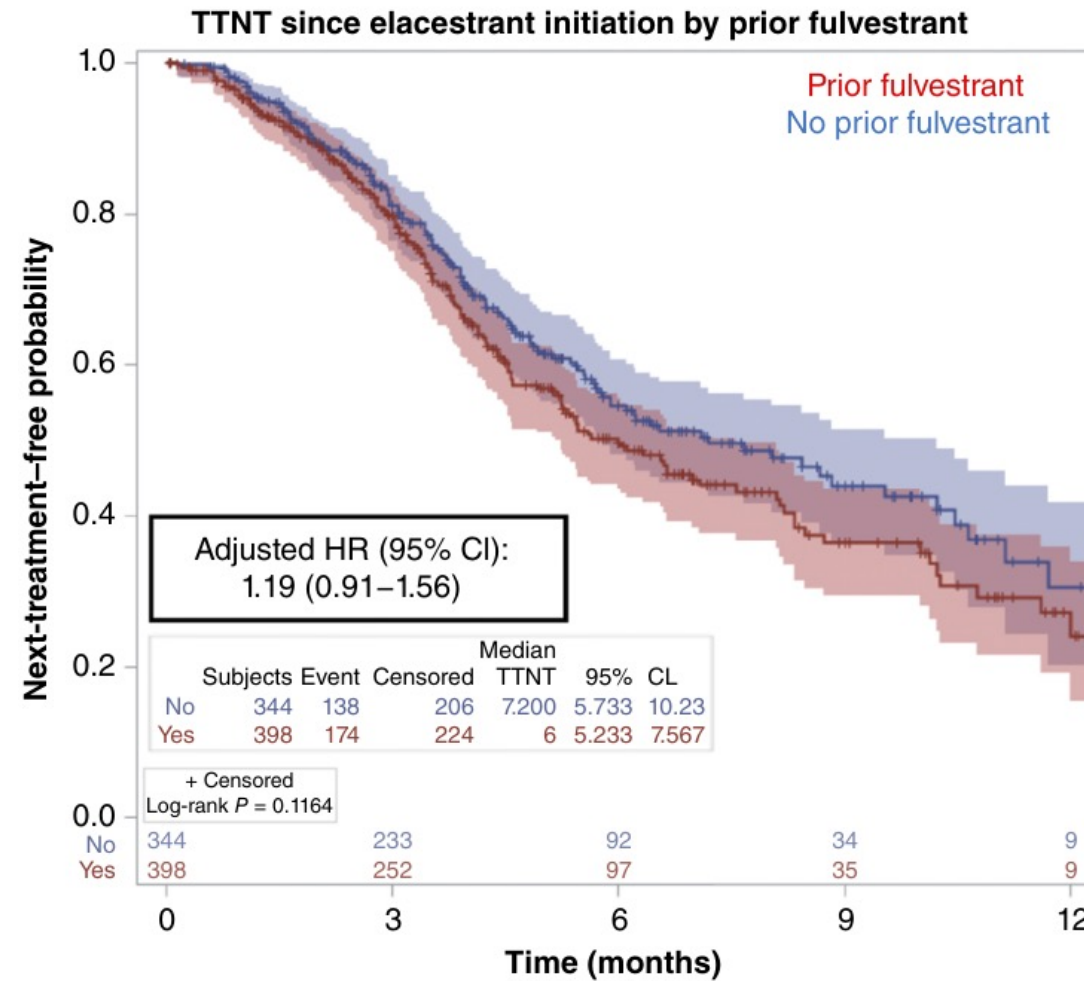
rwTTNT Since Elacestrant Initiation by Baseline PI3K Pathway Status



Patients without oncogenic PI3K pathway alterations showed to have a longer rwTTNT (8.0 mo vs 5.2 mo) compared to those having an alteration in this pathway.

Observational retrospective analyses are not intended for direct comparisons with clinical trials.

rwTTNT Since Elacestrant Initiation by Prior Fulvestrant



Patients without prior fulvestrant versus those with previous fulvestrant exposure trended toward better rwTTNT on elacestrant.

Observational retrospective analyses are not intended for direct comparisons with clinical trials.

Elacestrant real-world progression-free survival (rwPFS) of adult patients with ER+/HER2-, advanced breast cancer: A retrospective analysis using insurance claims in the United States

Komodo Research Database	
Study population	- Adults with diagnosed ER+/HER2- mBC who initiated elacestrant in a real-world setting were identified between January 2023 and February 2025. - Elacestrant is indicated for the treatment of postmenopausal women and men with ER+/HER2-, <i>ESR1</i>-mut, aBC or mBC with disease progression following at least 1 line of ET.
Genomic data	<i>ESR1</i>-mut status was not available in the Komodo Research Database at the time of analysis, but it was assumed patients received treatments according to their approved use.
Index date	Time of first administration of elacestrant
Demographic information at index date	- Metastatic sites identified during the 6-month baseline period prior to the index date - Prior treatments received in the mBC setting
Definition of rwPFS	Time from index date until earliest outcome (start of next line of therapy for mBC to disease progression or death) was assessed using time-to-event and Kaplan-Meier methods.
Censoring rule	- Patients were censored at first occurrence of: — end of data availability, OR — end of health plan enrollment.

Results: Overall Demographics and Clinical Characteristics

Observational retrospective analyses are not intended for direct comparisons with clinical trials.

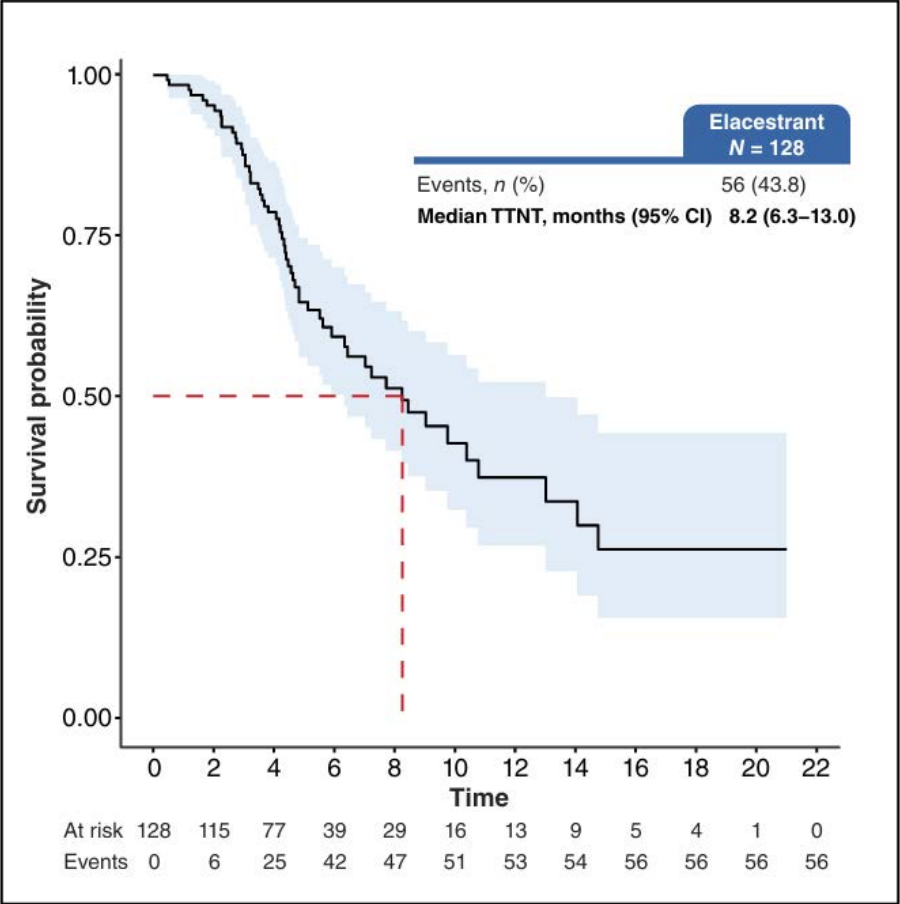
Rugo HS et al. CCR 2026

Table 1. Overall demographics and clinical characteristics.

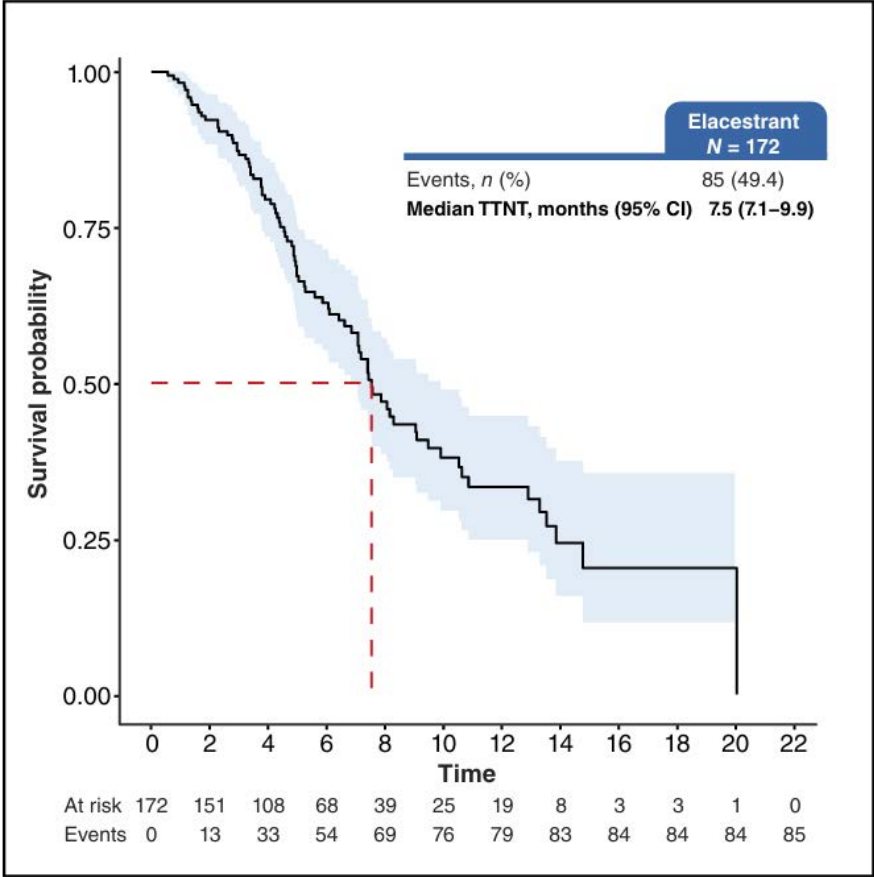
Parameters	<i>N</i> = 306
Median age (years) as of elacestrant initiation	64.4
Female, <i>n</i> (%)	301 (98.4)
Race/ethnicity, <i>n</i> (%)	
White (non-Hispanic)	197 (64.4)
Black or African American	34 (11.1)
Hispanic or Latino	23 (7.5)
Asian or Pacific Islander	13 (4.2)
Other	13 (4.2)
Unknown	8 (2.6)
Missing	18 (5.9)
Insurance type, <i>n</i> (%)	
Medicare	183 (59.8)
Commercial	92 (30.1)
Medicaid	29 (9.5)
Missing	2 (0.7)
Metastatic sites, <i>n</i> (%)	
Visceral metastasis	266 (86.9)
Liver	138 (45.1)
Lung	82 (26.8)
Brain and spinal cord	58 (19.0)
Bone/lymph node metastatic site only	37 (12.1)
Bone only	32 (10.5)
Lines of prior ET therapy in mBC, <i>n</i> (%)	
1–2 Lines	128 (41.8)
≥3 Lines	172 (56.2)
Prior mBC treatment use, <i>n</i> (%)	
ET	306 (100)
ET + CDK4/6i	275 (89.9)
ET alone	12 (3.9)
ET ± CDK4/6i ≥ 12 months	287 (93.8)
Fulvestrant	221 (72.2)
Chemotherapy	153 (50.0)
Genomic alterations, <i>n</i> (%)	
<i>ESR1</i> mutations	306 (100)
D538G	140 (45.8)
Y537(S/N/C)	154 (50.3)
Y537S	108 (35.3)
E380Q	27 (8.8)
Number of <i>ESR1</i> mutation variants	
1	244 (79.7)
≥2	62 (20.3)
<i>PIK3CA</i> mutations	133 (43.5)
H1047 variants	61 (19.9)
E545 variants	34 (11.1)
E542K variant	19 (6.2)
<i>PTEN</i> loss	21 (6.9)
<i>AKT</i> alteration	18 (5.9)

mmTTNT Benefit in the Overall Population by Number of Prior Lines of ET

1–2 Prior lines of ET ± CDK4/6i



≥3 Prior lines of ET ± CDK4/6i



Observational retrospective analyses are not intended for direct comparisons with clinical trials.

mmTTNT Benefit in Relevant Subgroups

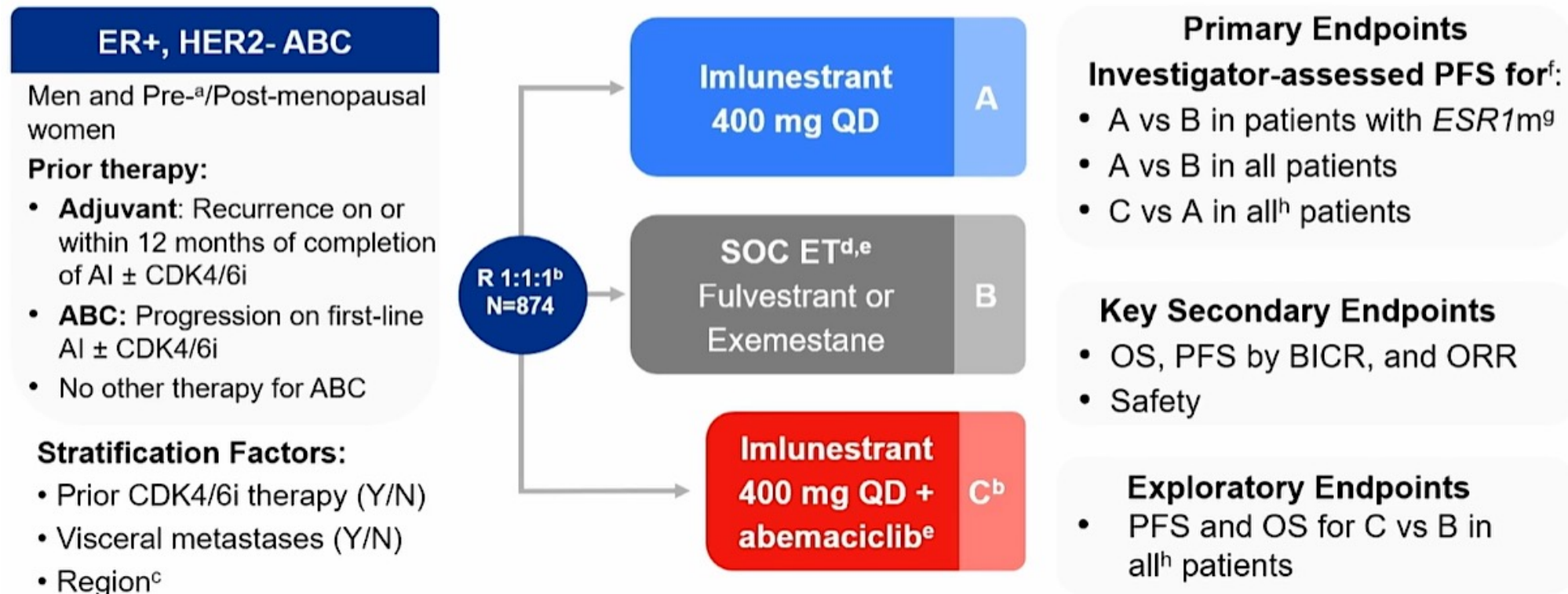
Table 2. mTTNT benefit in relevant subgroups.

Patient subgroups	N (%)	No. of events (%)	mTTNT (95% CI), months
1-2 Prior lines of ET ± CDK4/6i	128 (41.8)	56 (43.8)	8.2 (6.3, 13.0)
1-2 Prior lines of ET ± CDK4/6i ≥ 12 months	116 (37.9)	49 (42.2)	8.4 (6.3, 14.1)
1 Prior line of ET ± CDK4/6i	56 (18.3)	22 (39.3)	10.8 (5.9, NR)
2 Prior lines of ET ± CDK4/6i	72 (23.5)	34 (47.2)	7.7 (4.8, 13.0)
≥3 Prior lines of ET ± CDK4/6i	172 (56.2)	85 (49.4)	7.5 (7.1, 9.9)
Visceral metastasis	266 (86.9)	122 (45.9)	7.9 (7.0, 9.9)
Coexisting <i>ESR1</i> and <i>PI3K</i> -pathway mutations ^a	130 (42.5)	75 (57.7)	6.3 (4.8, 7.9)
No prior fulvestrant	85 (27.8)	33 (38.8)	12.9 (7.2, NR)
No prior chemotherapy	153 (50.0)	64 (41.8)	8.4 (7.1, 13.3)

^aIncludes patients with at least one *ESR1* mutation variant (*Y537C*, *Y537N*, *Y537S*, *D538G*, and/or *E380Q*) and at least one *PIK3CA* mutation variant (*H1047*, *E545*, and/or *E542*), *AKT* alteration, or *PTEN* loss of function.

EMBER-3: PH 3 Trial Fulvestrant vs Imlunestrant +/- Abemaciclib

SERD: Imlunestrant

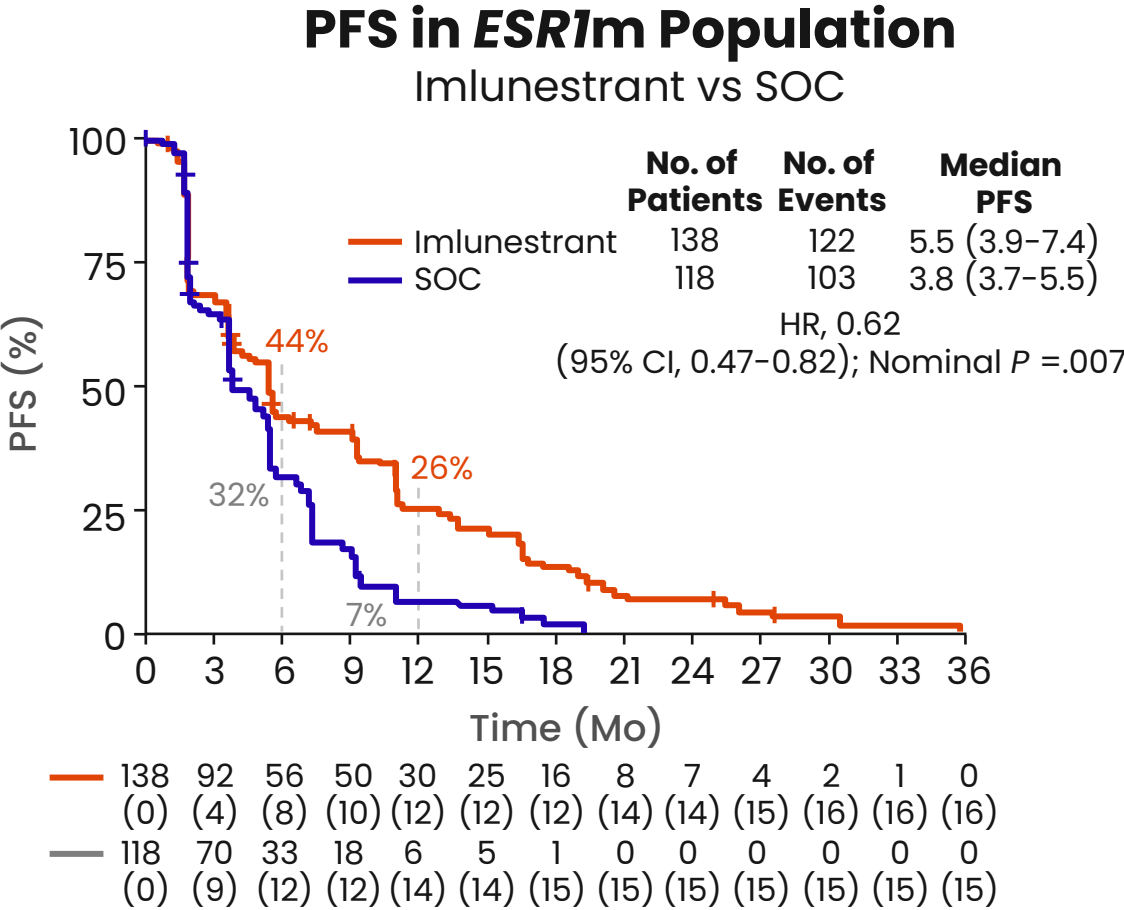


EMBER-3: Baseline Patient Characteristics

Characteristic	Imlunestrant n=331	SOC ET n=330	Imlunestrant + abemaciclib n=213
Median age, years (range)	61 (28-87)	62 (27-89)	62 (36-87)
Female, %	99	99	99
Post-menopausal, %	84	86	86
Race, %			
White	56	58	52
Asian	28	29	34
Black or African American	3	2	4
Region, %			
East Asia	25	26	31
North America/Western Europe	38	39	45
Other	37	36	24
PR-positive, %	78	79	74
ESR1 mutation, % ^a	42	36	32
PI3K pathway mutations, % ^b	39	39	41

Characteristic	Imlunestrant n=331	SOC ET n=330	Imlunestrant + abemaciclib n=213
Site of metastases, %			
Visceral	57	54	56
Liver	32	30	27
Bone-only	22	26	24
Endocrine resistance, % ^c			
Primary	8	11	8
Secondary	92	89	93
Most recent ET, % ^d			
Adjuvant	32	34	30
ABC	63	63	68
Overall	59	57	65
Previous CDK4/6i, %			
Adjuvant	4	5	3
ABC	55	53	62
Previous CDK4/6i therapy, % ^e			
Palbociclib	61	69	65
Ribociclib	29	27	27
Abemaciclib	10	4	7

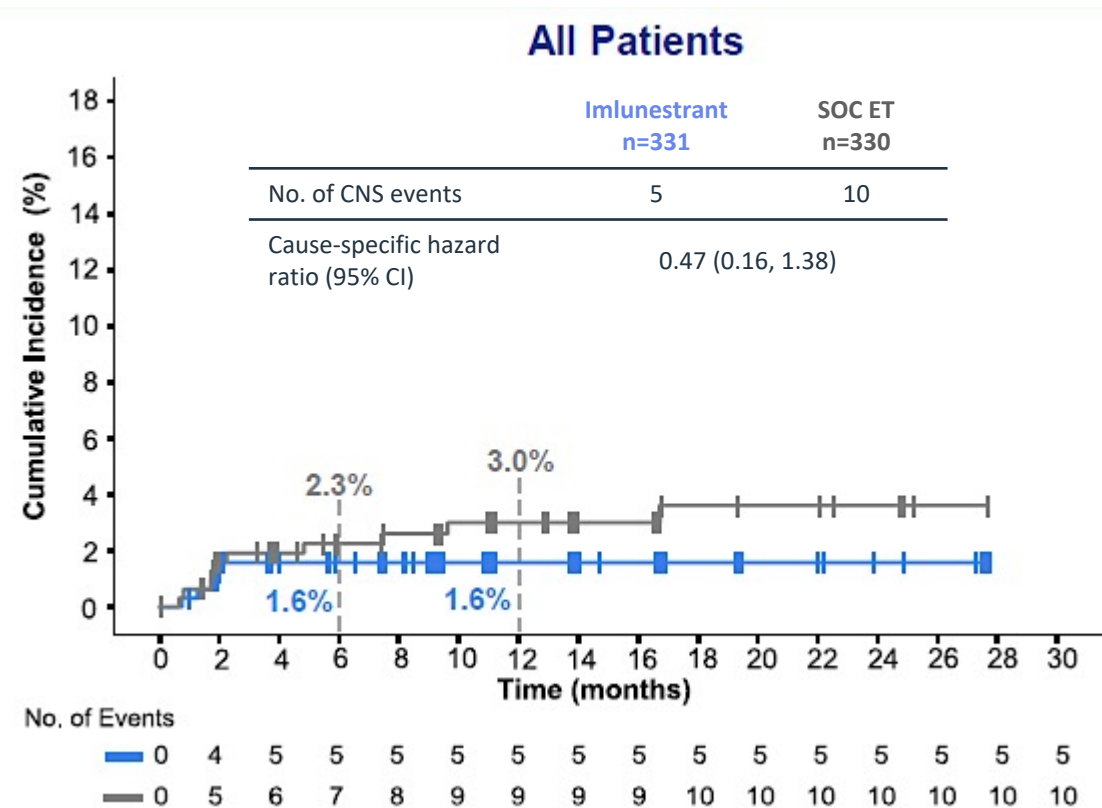
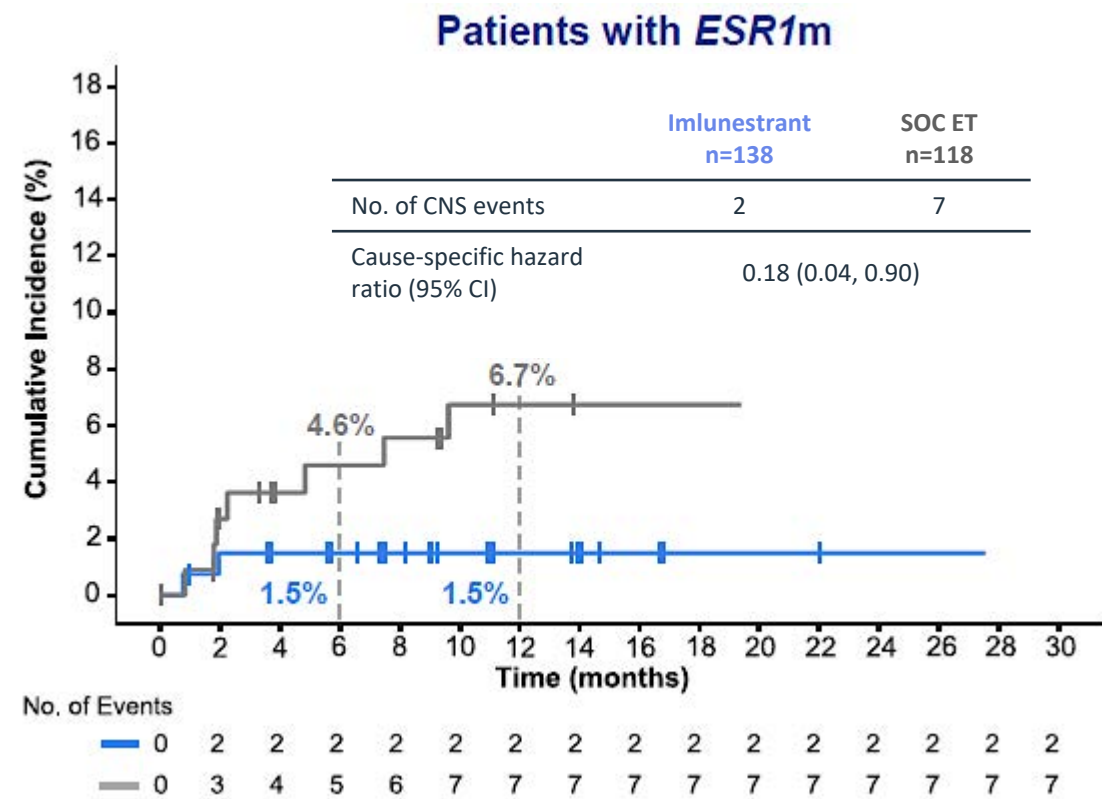
EMBER-3 Update: PFS (Primary Endpoint)



ESR1m: PFS benefit sustained with imlunestrant at median follow-up of 27.6 mo

EMBER-3: Posthoc exploratory analysis, imlunestrant vs SOC ET

cumulative incidence rates of CNS progression

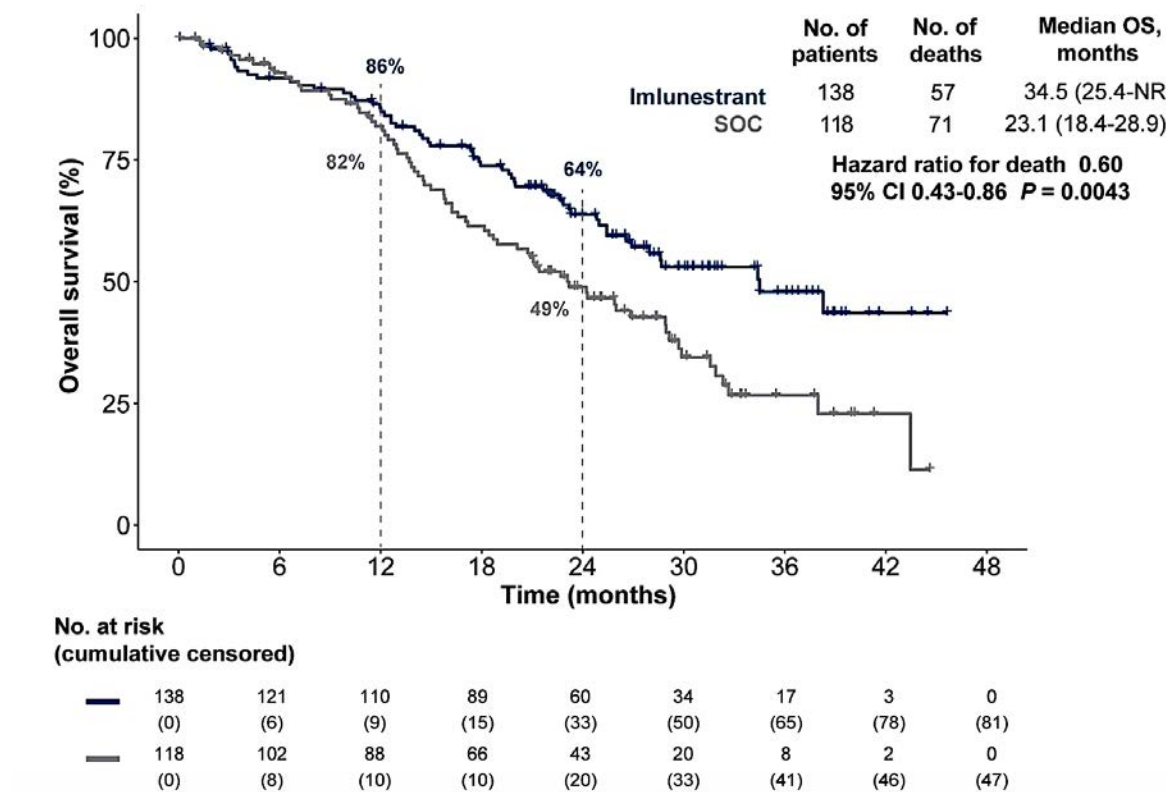


EMBER-3 Subgroup Analysis: PFS by Subgroup

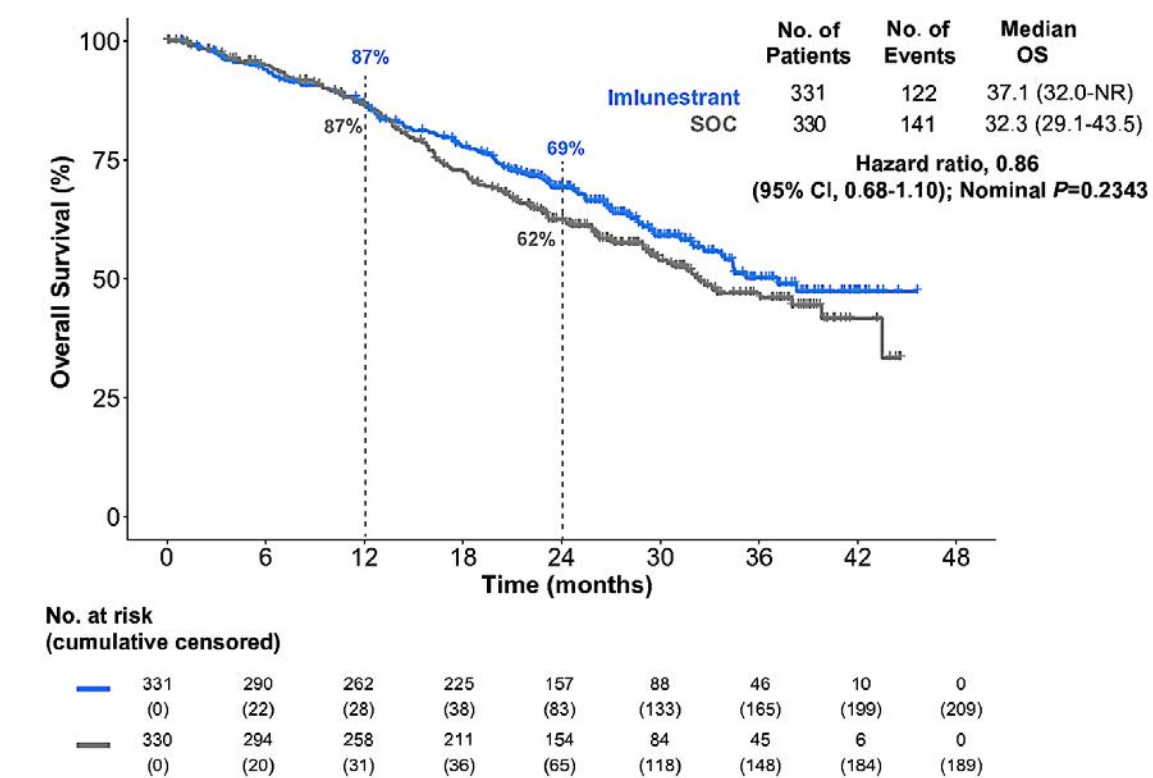
Subgroup	Patients, n (%)	Median PFS, Mo (95% CI)		HR (95% CI)
		Imlunestrant-abemaciclib	Imlunestrant	
With <i>ESR1</i> m	159	11.1	5.5	0.49 (0.33-0.71)
Without <i>ESR1</i> m	267	9.2	5.5	0.59 (0.47-0.85)
With <i>PIK3CA</i> m	172	7.6	3.8	0.57 (0.41-0.80)
Without <i>PIK3CA</i> m	221	11.3	5.6	0.59 (0.43-0.81)
<i>ESR1</i> m and <i>PI3K</i> m	68	16.4	3.8	0.29 (0.15-0.53)

EMBER-3: Updated OS

Patients with *ESR1m*



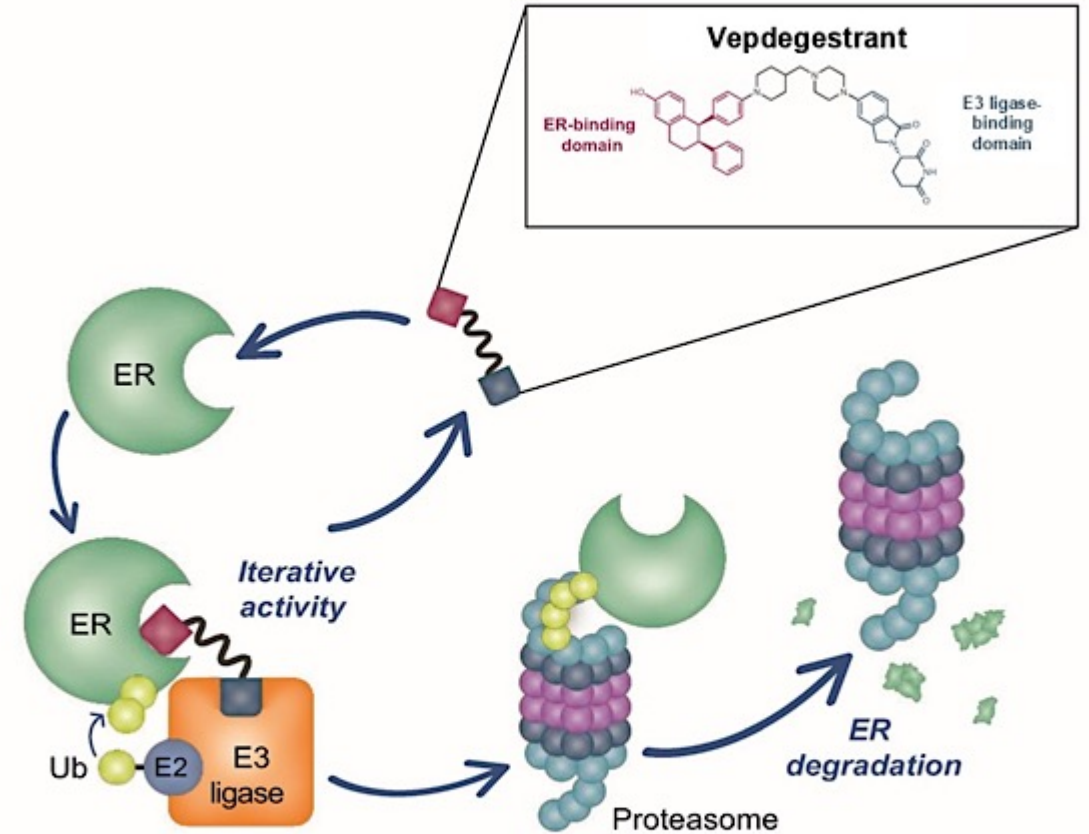
All patients



Median follow-up of 29.5 months

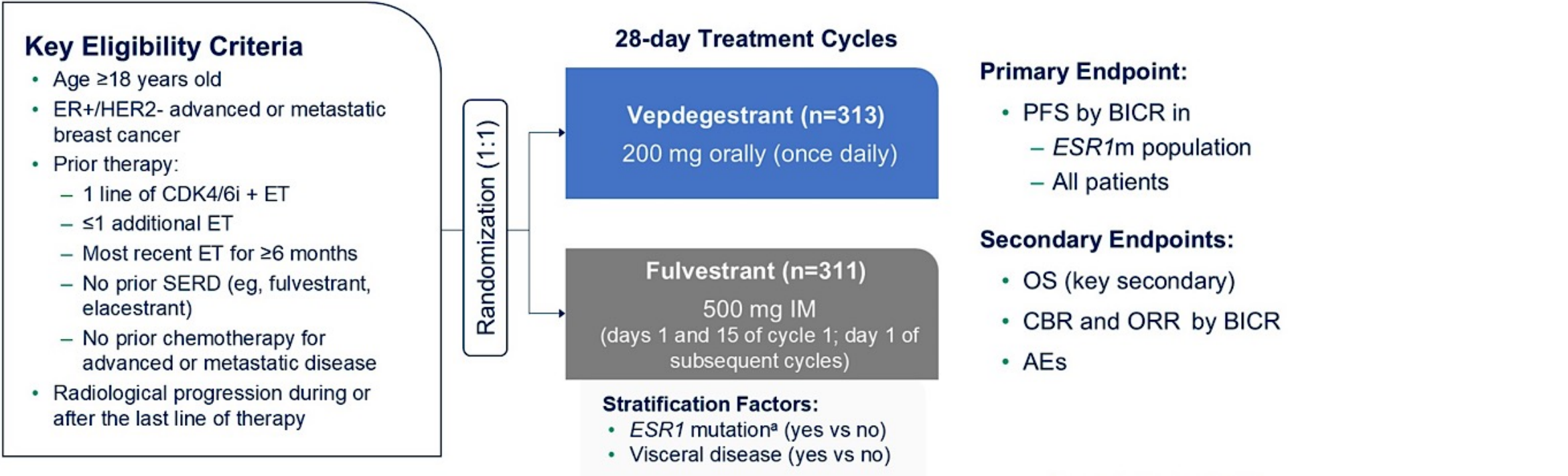
Vepdegestrant – PROTAC ER degrader

- There is a need for effective ET based treatment for HR+/HER2- MBC after progression on 1L ET+ CDK 4/6i
- Fulvestrant, a selective ER degrader (SERD) has limited PFS benefit as 2L therapy (mPFS 1.8 months) and has to be administered IM
- **Vepdegestrant** is a selective oral PROTAC ER degrader that targets WT and mutant ER



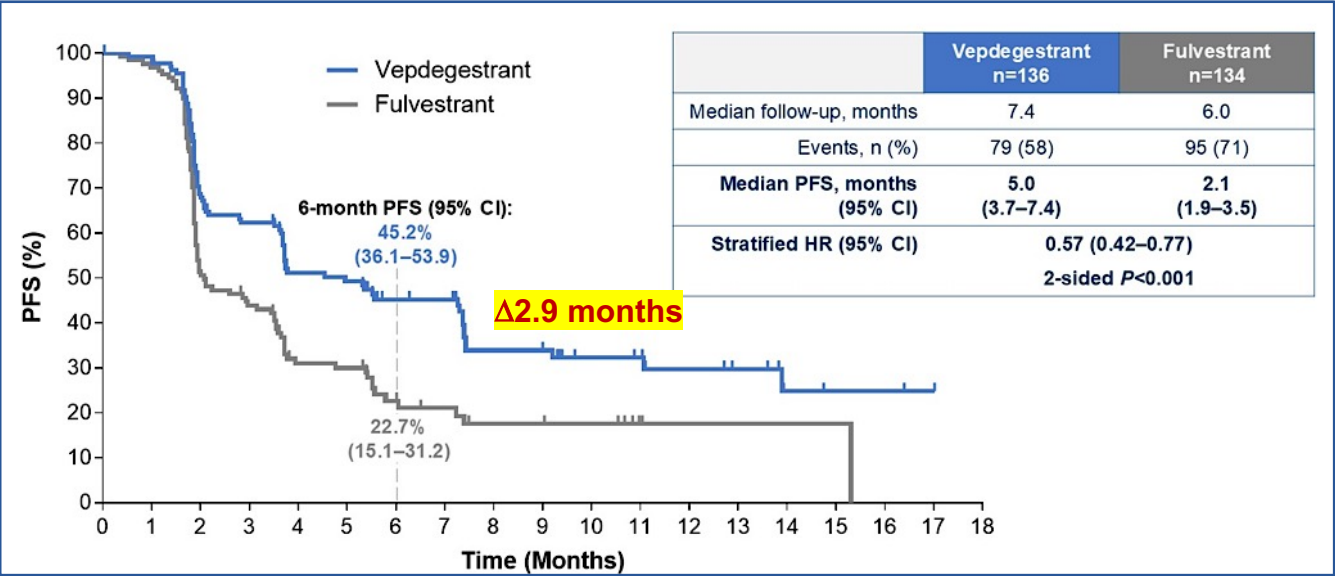
Vepdegestrant has a unique MOA that directly harnesses the ubiquitin-proteasome system to degrade ER⁸

VERITAC-2: Ph 3 trial of Vepdeg vs Fulv post CDK4/6i + ET



VERITAC-2: Ph 3 trial of Vepdeg vs Fulv post CDK4/6i + ET

PFS in *ESR1* mutant population



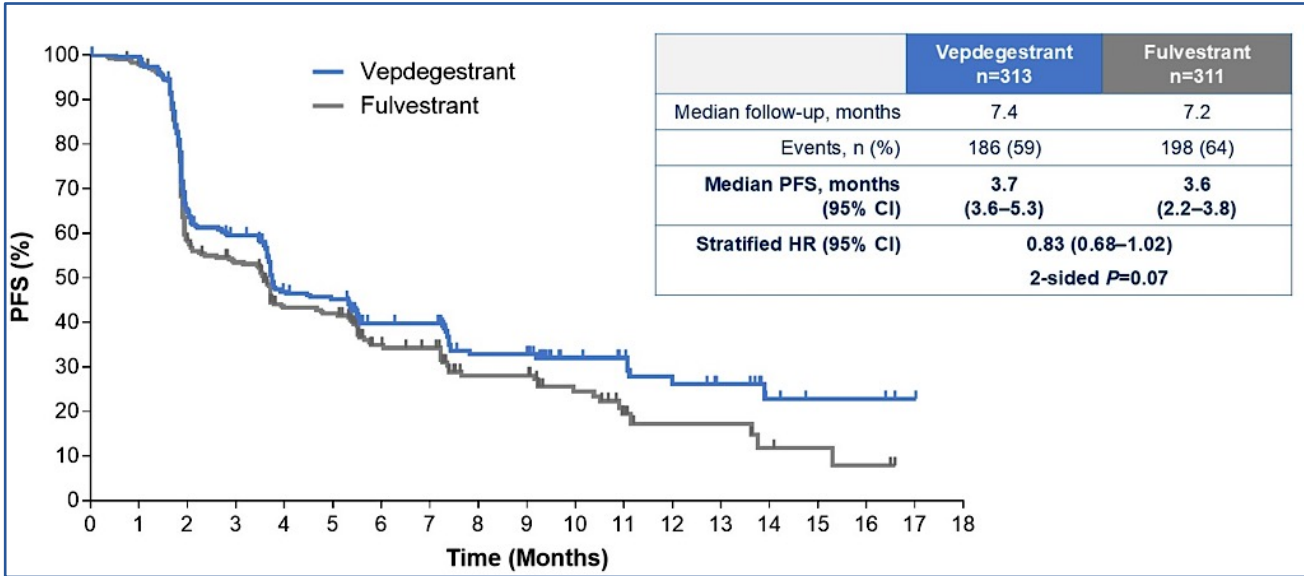
Vepdeg treatment results in clinically meaningful and statistically significant improvement in mPFS in the *ESR1m* HR+/HER2- MBC

Safety:

Most common AE was fatigue (27% all grade)
Vomiting and diarrhea any grade=6%

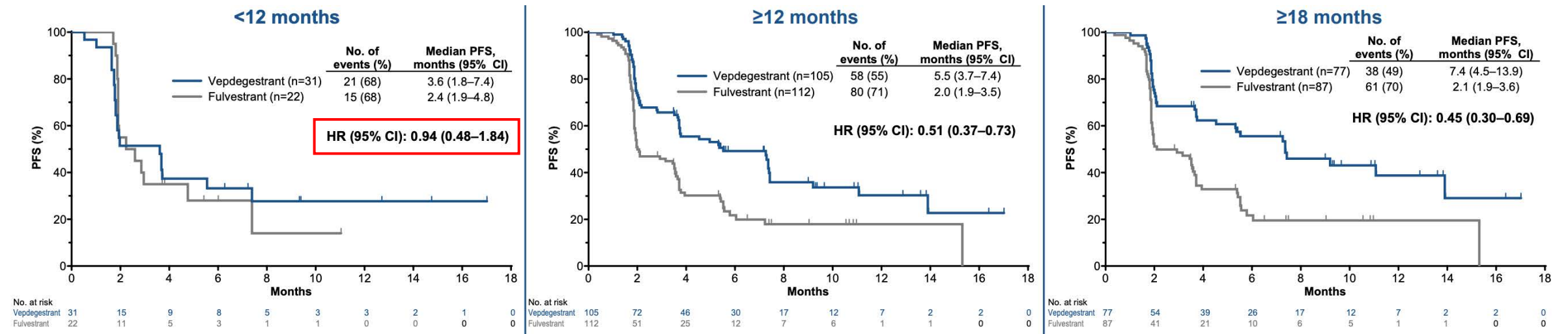
Very low rates of dose reductions and treatment discontinuations

PFS in all patients

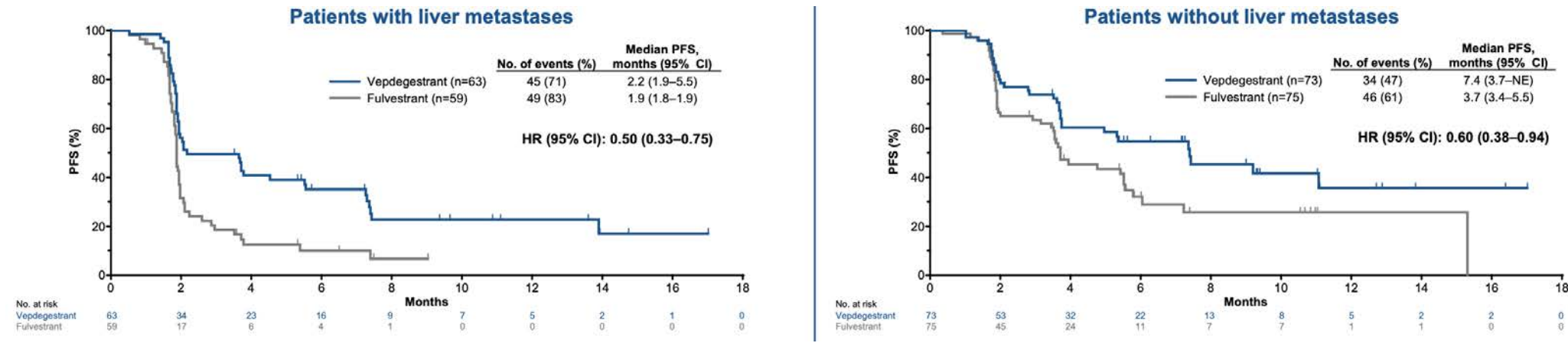


VERITAC-2: Subgroup analysis in ESR1_{mut} HR+/HER2- mBC

Duration of prior CDK4/6i



Presence of liver mets



Summary of toxicity profiles

Drug	Common AEs (all grades)
Elacestrant	Nausea, vomiting, fatigue, dyspepsia, arthralgia, metabolic effect
Imlunestrant	Nausea, fatigue, diarrhea , arthralgia
Camizestrant	Visual changes , bradycardia , nausea, fatigue
Giredestrant	Fatigue, arthralgia, nausea, bradycardia
Vepdegestrant	Nausea, fatigue, vomiting
Palazestrant	Nausea, fatigue, vomiting, constipation, neutropenia

PHASE 3 oral SERD/PROTAC studies

	Elacestrant	Imlunestrant	Vepdegestrant
Study name	EMERALD	EMBER-3	VERITAC-2
Total n	477	834	634
Post-CDK	100%	60%	100%
Prior SERD	30.4%	0%	0%
Prior chemo	22%	0%	0%
<i>ESR1mut</i> PFS	3.8 mo elacestrant vs 1.9 mo SOC	5.5 mo imlunestrant vs 3.8 mo SOC ET	5.0 mo vepdeg vs 2.1 mo SOC ET
Hazard Ratio	0.55	0.62	0.57
G3/4 AEs	27% elacestrant vs 20.5 % SOC	17.1% imlunestrant vs 20.7% SOC	23% vepdegestrant vs 18% SOC
Dose reductions	3.0% elacestrant vs NA SOC	2.4% imlunestrant vs NA SOC	2% vepdegestrant vs NA SOC
Dose discontinuations	6.3% elacestrant vs 4.4% SOC	4.3% imlunestrant vs 1.2% SOC	3% vepdegestrant vs 1% SOC

Which treatment would you recommend next for a 65-year-old woman (PS 0) with ER/PR-positive, HER2-low (IHC 1+) mBC who develops multiple minimally symptomatic bone metastases after receiving ribociclib/letrozole?

Her biomarker testing results are:

- **PIK3CA/AKT1/PTEN-negative**
- **ESR1-positive**
- **BRCA wild type**

Age 65, PS 0; HER2-low (IHC 1+) BRCA wild-type mBC
Multiple minimally symptomatic bone metastases
PIK3CA/AKT1/PTEN-negative, ESR1-positive

		After receiving ribociclib/letrozole for 2 years	After receiving ribociclib/letrozole for 10 months
	Dr Hurvitz	Elacestrant, imlunestrant or vepdegestrant — no preference	Everolimus + fulvestrant
	Dr Mayer	Elacestrant, imlunestrant or vepdegestrant	Imlunestrant + abemaciclib
	Dr O'Shaughnessy	Elacestrant	Imlunestrant + abemaciclib but imlunestrant if need to choose monoRx
	Dr Tolaney	Elacestrant, imlunestrant or vepdegestrant — no preference	Imlunestrant + abemaciclib
	Dr Turner	Elacestrant	Everolimus + fulvestrant
	Dr Kaklamani	Elacestrant	Imlunestrant + abemaciclib

Which treatment would you recommend next for an 80-year-old woman (PS 2) with ER/PR-positive, HER2-low (IHC 1+) mBC who develops multiple minimally symptomatic bone metastases after receiving ribociclib/letrozole for 2 years?

Her biomarker testing results are:

- **PIK3CA-positive**
- **ESR1-positive**
- **BRCA wild type**

Age 80, PS 2; HER2 IHC 1+, BRCA wild-type mBC

Received ribociclib/letrozole for 2 years; multiple minimally symptomatic bone metastases

PIK3CA/AKT1/PTEN-positive, ESR1-positive



Dr Hurvitz

Elacestrant



Dr Mayer

Elacestrant



Dr O'Shaughnessy

Elacestrant



Dr Tolaney

Elacestrant



Dr Turner

Elacestrant



Dr Kaklamani

Elacestrant

A 65-year-old woman presents with de novo ER/PR-positive, HER2 IHC 1+, BRCA wild-type mBC, receives ribociclib with letrozole and initially responds but then experiences disease progression 18 months later. Biomarker evaluation is negative for ESR1 mutations and PIK3CA/AKT1/PTEN alterations. She then receives abemaciclib with fulvestrant with response followed by disease progression 8 months later. Repeat biomarker evaluation reveals an ESR1 mutation and is negative for PIK3CA/AKT1/PTEN alterations.

What treatment would you most likely recommend next?

Age 65, PS 0; first-line ribociclib/letrozole, PD 18 months later; abemaciclib and fulvestrant, PD 8 months later, new ESR1 mutation detected
PIK3CA/AKT1/PTEN-negative, BRCA wild type



Dr Hurvitz

Elacestrant, imlunestrant or vepdegestrant — no preference



Dr Mayer

Elacestrant, imlunestrant or vepdegestrant



Dr O'Shaughnessy

Imlunestrant



Dr Tolaney

Elacestrant, imlunestrant or vepdegestrant



Dr Turner

Elacestrant



Dr Kaklamani

Elacestrant

Will you use oral SERD monotherapy or vepdegestrant first for your patients with HR-positive, HER2-negative mBC and an ESR1 mutation?



Dr Hurvitz

Oral SERD monotherapy



Dr Mayer

Oral SERD monotherapy



Dr O'Shaughnessy

Oral SERD monotherapy



Dr Tolaney

Oral SERD monotherapy



Dr Turner

Oral SERD monotherapy



Dr Kaklamani

Oral SERD monotherapy

How would you indirectly compare the global efficacy of elacestrant and imlunestrant when employed as monotherapy for patients with endocrine therapy-pretreated, HR-positive, HER2-negative mBC with an ESR1 mutation?



Dr Hurvitz

About the same



Dr Mayer

About the same



Dr O'Shaughnessy

Imlunestrant is more efficacious



Dr Tolaney

About the same



Dr Turner

About the same



Dr Kaklamani

About the same

Agenda

Module 1: Current and Future Roles of Agents Targeting the PI3K/AKT/mTOR Pathway and Oral SERDs in First-Line Therapy for HR-Positive, HER2-Negative Metastatic Breast Cancer (mBC) — Dr Turner

Module 2: Role of Oral SERD Monotherapy in the Treatment of Progressive HR-Positive, HER2-Negative mBC — Dr O'Shaughnessy

Module 3: Potential Use of Oral SERD-Containing Combination Regimens in Managing Progressive HR-Positive, HER2-Negative mBC — Dr Mayer

Module 4: Clinical Utility of Agents Targeting the PI3K/AKT/mTOR Pathway for Patients with Progressive HR-Positive, HER2-Negative mBC — Dr Hurvitz

Module 5: Potential Use of Oral SERDs for HR-Positive, HER2-Negative Localized BC — Dr Tolaney

May 2026

Potential Use of Oral SERD-Containing Combination Regimens in Progressive HR-Positive, HER2-Negative mBC

Erica L. Mayer MD, MPH

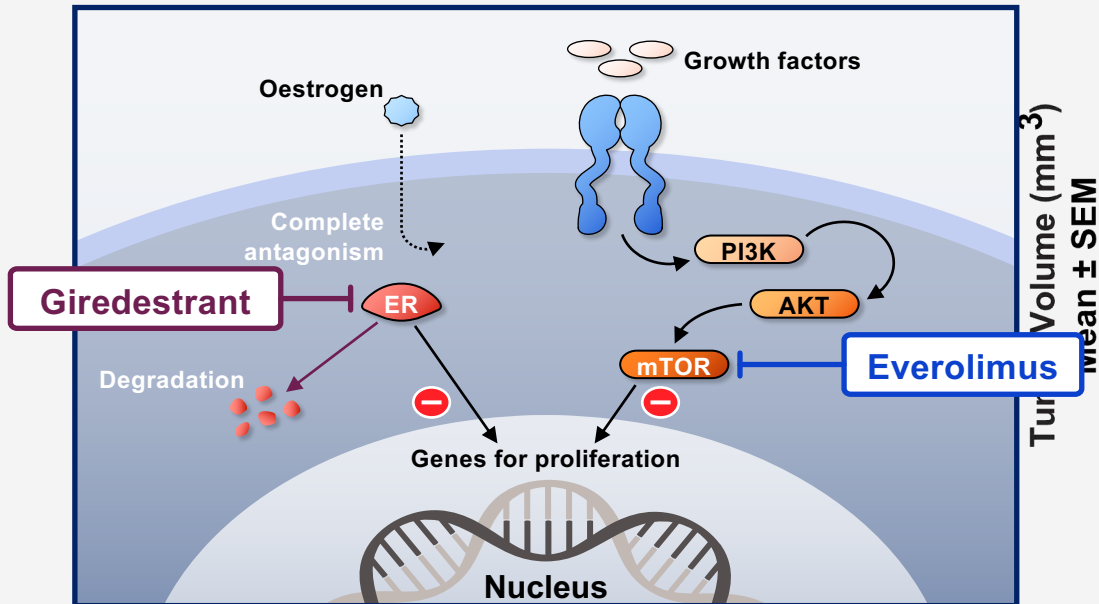
Division of Breast Oncology
Dana-Farber Cancer Institute



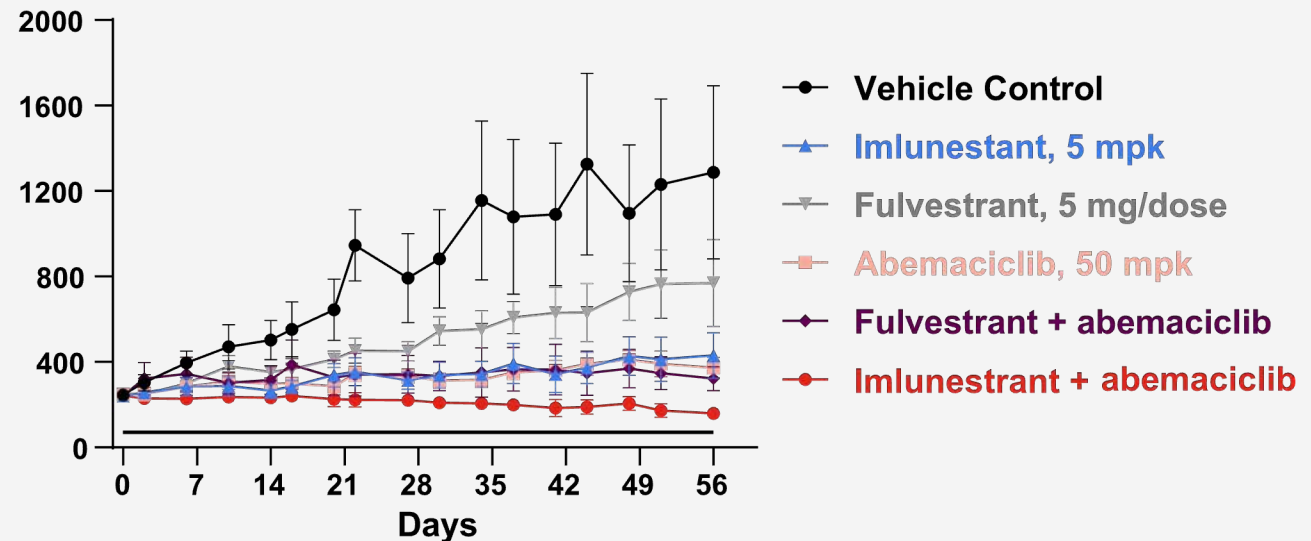
Why Consider Oral SERD Combinations?

- **Multiple signaling pathways are active in the setting of endocrine resistance** in ER+ HER2- breast cancer, including ER, CDK4/6, and PIK3CA/AKT/mTOR.
- Continued and comprehensive **suppression of signaling pathways beyond progression** on CDK4/6i + ET may improve patient outcomes.
- **Co-targeting with oral SERD and targeted partner** may provide synergistic activity and overcome resistance.

Giredestrant + everolimus mechanism of action



In Vivo Efficacy Imlunestant in CTG-1260 *ESR1 D538G* Model



VandeKopple M, et al. ESMO Breast 2023. Abstract 41P.

Erica L. Mayer, MD, MPH | ASCO 2026

Phase III Trials Evaluating Oral SERD Combinations in MBC

Trials in MBC	Oral SERD	Line of Therapy	Trial Population	Therapy Partner
EMBER-3	Imlunestrant	1L/2L	Endocrine resistant	+ Abemaciclib
persevERA	Giredestrant	1L	Endocrine sensitive	+ Palbociclib
pionERA		1L	Endocrine resistant	+ CDK4/6i
evERA		2L+	Prior ET + CDK4/6i; endocrine resistant	+ Everolimus
SERENA-4	Camizestrant	1L	De novo or recurrent stage IV disease; endocrine sensitive	+ Palbociclib
SERENA-6		1.5L	Patients currently receiving AI + CDK4/6i with emergence of <i>ESR1</i> mut	+ CDK4/6i

Oral SERDs as Monotherapy for Pretreated HR+/HER2-MBC: EMBER-3 Phase 3 Study

KEY ELIGIBILITY CRITERIA

- ER+/HER2- MBC
- 1-2 prior lines of ET +/- CDK4/6i (60%)
- ≤1 line of chemotherapy for MBC

R
A
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D

1:1:1
N=874

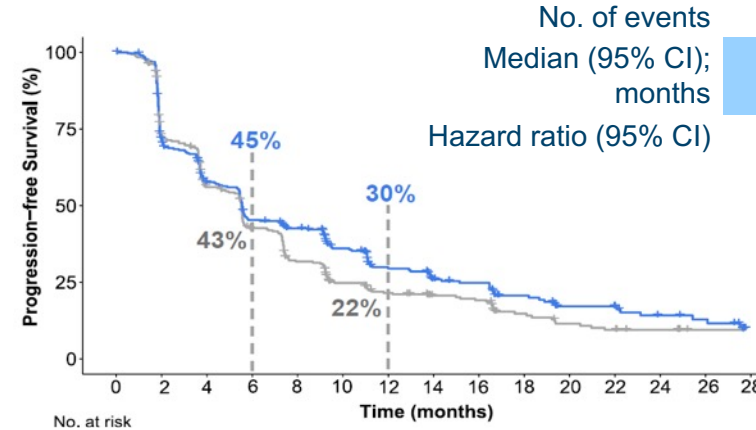
Imlunestrant

SOC ET

Imlunestrant + abemaciclib

Primary endpoints^c: PFS imlu vs SOC ITT, Imlu vs SOC ESR1, imlu + abema vs imlu ITT,
Secondary endpoints: OS, safety

ITT



No. of events
Median (95% CI);
months
Hazard ratio (95% CI)

Imlunestrant
n=331

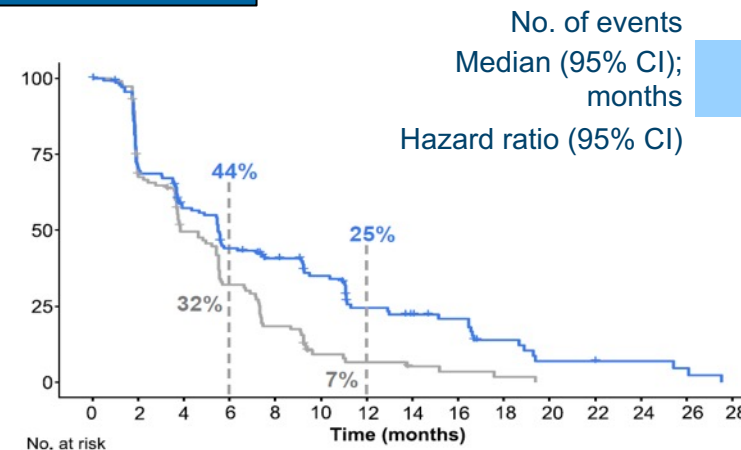
237
5.6
(5.3–7.3)

SoC ET
n=330

253
5.5
(4.6–5.6)

0.87 (0.72–1.04)
p-value 0.12

ESR1m



No. of events
Median (95% CI);
months
Hazard ratio (95% CI)

Imlunestrant
n=138

109
5.5
(3.9–7.4)

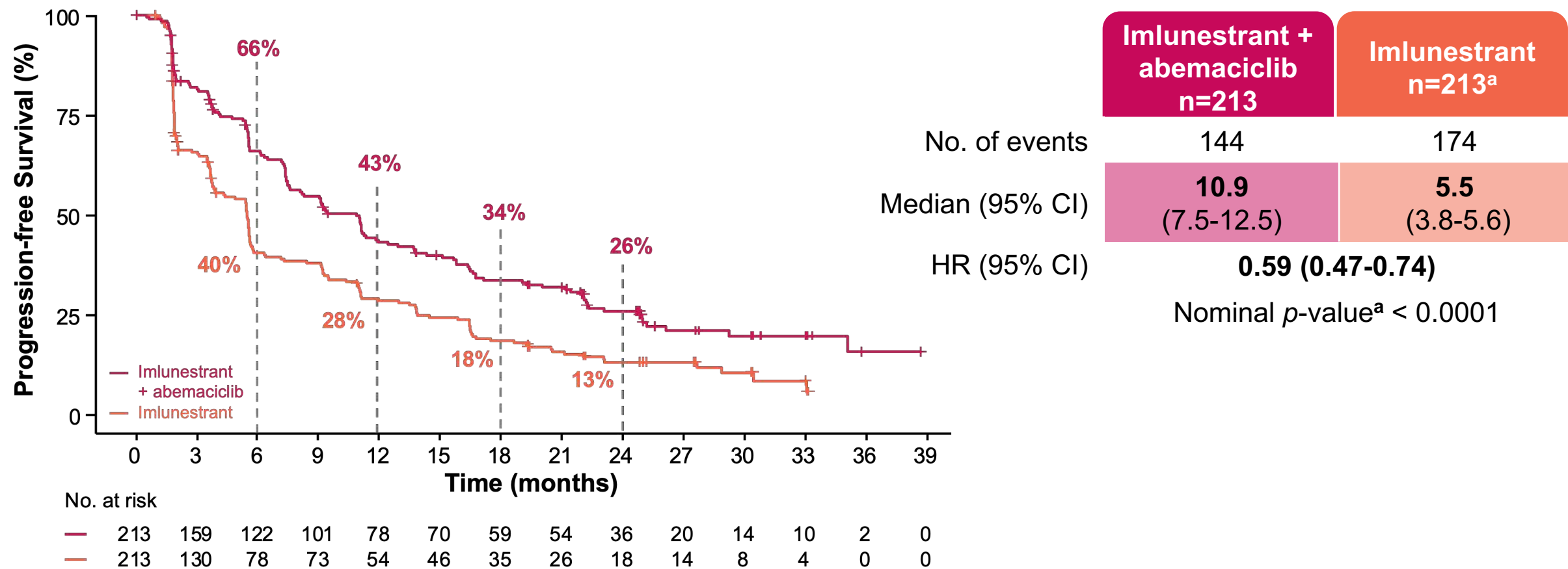
SoC ET
n=118

102
3.8
(3.7–5.5)

0.62 (0.46–0.82)
p-value <0.001

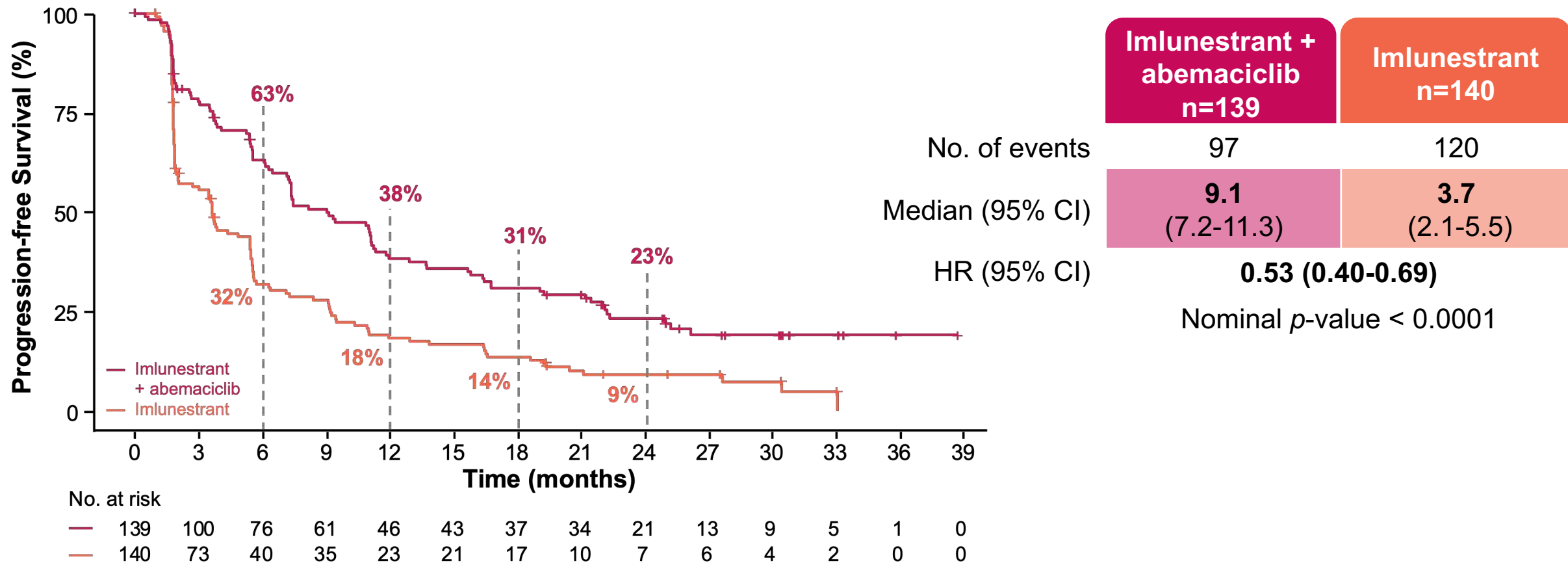
DCO: 24 June 2024. *Median follow-up for patients with ESR1m was 16.7 months (imlunestrant group) and 13.8 months (SoC ET group); †Median follow-up for all patients was 16.6 months (imlunestrant group) and 16.8 months (SoC ET group); ‡At full alpha after recycling. CI=confidence interval; DCO=data cutoff; ESR1m=estrogen receptor 1 mutation; ET=endocrine therapy; PFS=progression-free survival; SoC=standard of care. Jhaveri KL, et al. *N Engl J Med* 2025; 392(12):1189-1202.

EMBER-3 Primary Endpoint: PFS of Imlunestrant + Abemaciclib vs Imlunestrant in All Patients



PFS benefit of imlunestrant + abemaciclib was maintained in all patients.

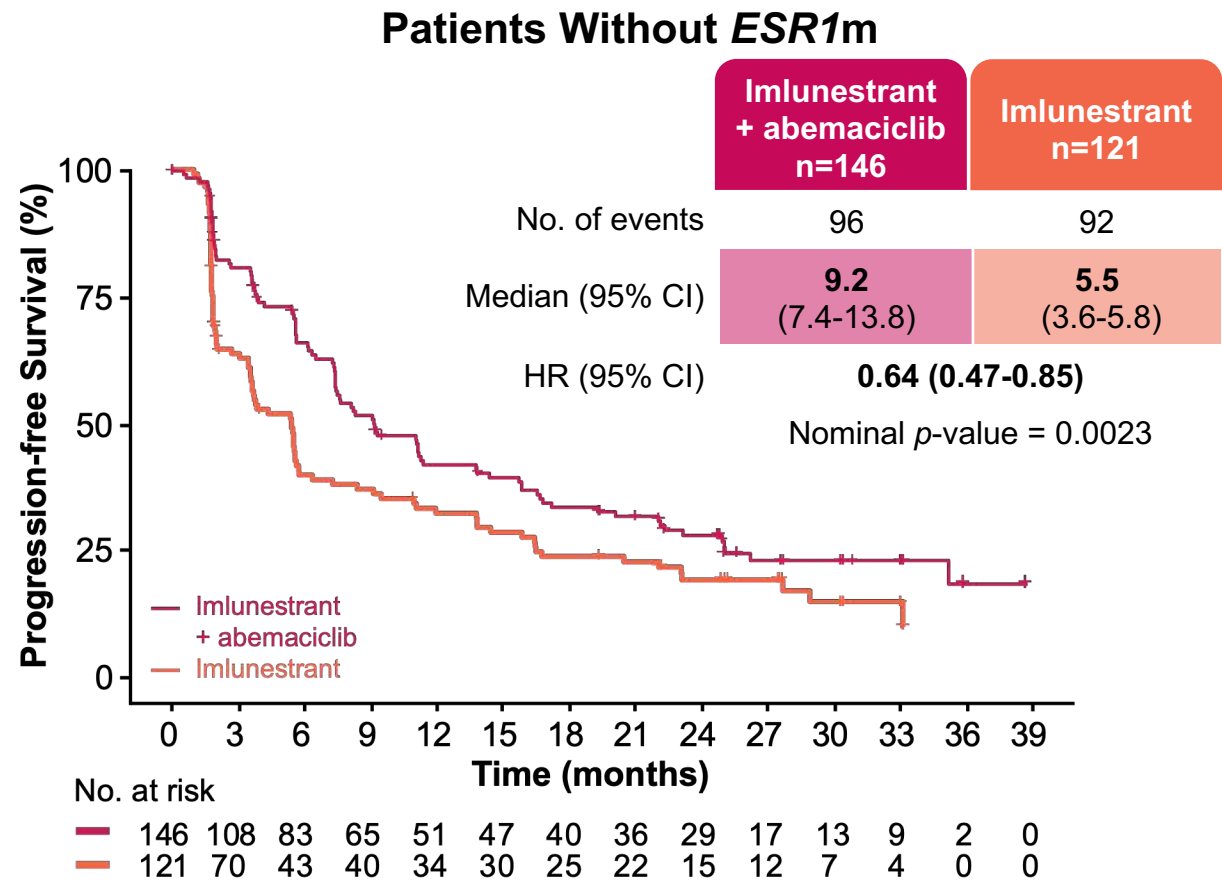
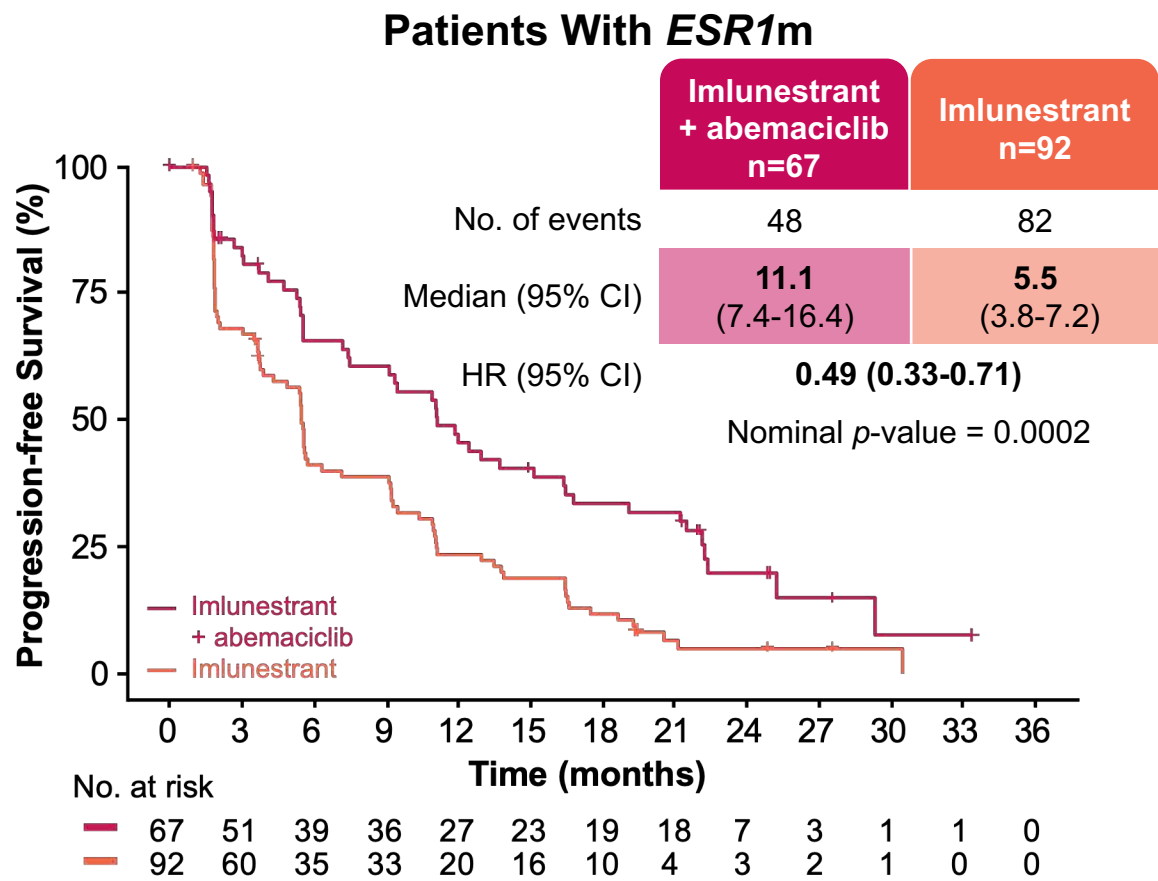
Subgroup Analysis: PFS of Imlunestrant + Abemaciclib vs Imlunestrant in CDK4/6i Pretreated Patients



Consistent benefit of imlunestrant + abemaciclib maintained in patients previously treated with a CDK4/6i.

CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

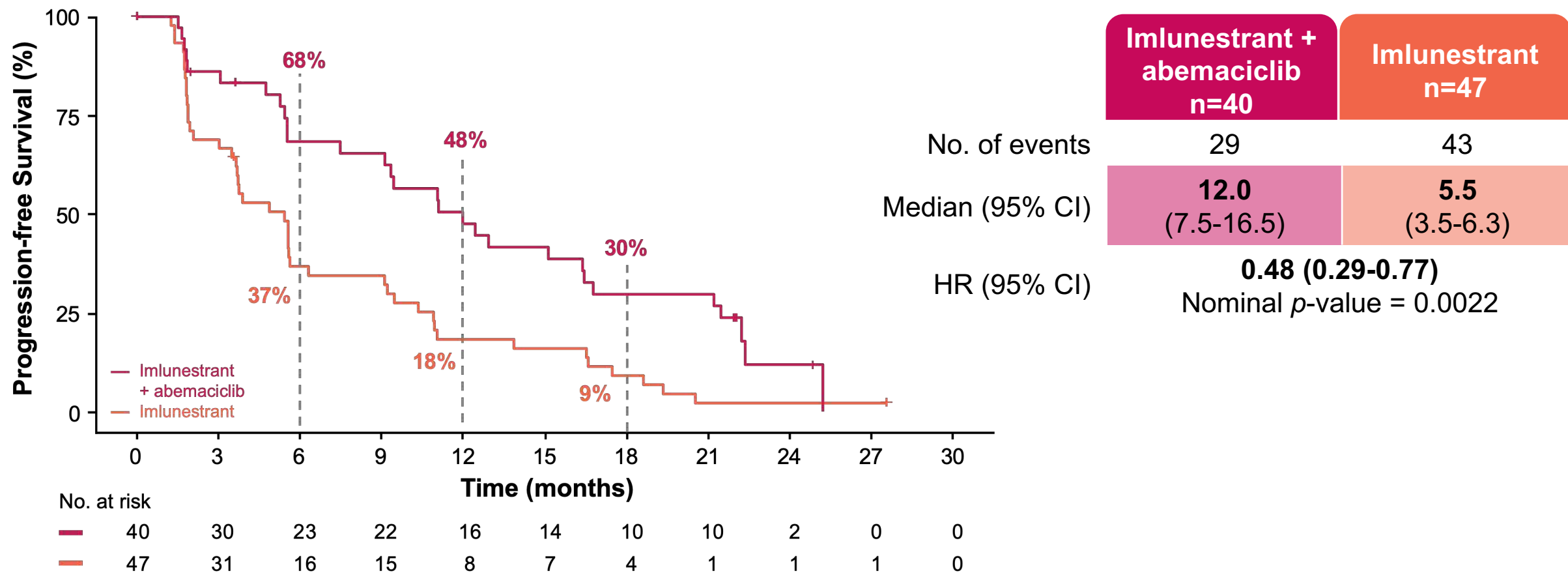
EMBER-3 Subgroup Analysis: PFS of Imlunestrant + Abemaciclib vs Imlunestrant by *ESR1m* Status



Consistent benefit of imlunestrant + abemaciclib maintained regardless of *ESR1m* status. Combining a novel endocrine agent with targeting of cross-talk resistance pathway may increase efficacy and overcome dependence on *ESR1m*.

CI, confidence interval; *ESR1m*, estrogen receptor 1 gene mutation; HR, hazard ratio; PFS, progression-free survival.

EMBER-3 Subgroup Analysis: PFS of Imlunestrant +Abemaciclib vs Imlunestrant in Patients With *ESR1*m and PI3K Pathway Mutation^a



Consistent PFS benefit with imlunestrant + abemaciclib in patients with *ESR1*m and PI3K pathway mutation.

EMBER-3: Safety and Tolerability

TEAEs in ≥ 25% of Patients, %	Imlunestrant + abemaciclib n=208		Imlunestrant n=327		SOC ET n=324	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with ≥1 TEAE	98	54	85	20	85	22
Diarrhea	86	9	23	<1	12	0
Neutropenia	50	22	6	3	5	2
Nausea	50	2	18	<1	14	0
Anemia	46	10	11	2	13	3
Fatigue	41	5	24	<1	14	1
Vomiting	32	<1	9	1	5	<1
Leukopenia	29	4	6	1	5	0
Hypercreatininemia	25	1	4	<1	3	0
TEAEs leading to discontinuation	9		5		1	
Treatment-related	5		2		0	

The safety profiles remained consistent with the known characteristics of imlunestrant and abemaciclib.

SOC ET, standard of care endocrine therapy; TEAE, treatment-emergent adverse event.



NCCN Guidelines Version 1.2026

Invasive Breast Cancer

SYSTEMIC THERAPY FOR ER- AND/OR PR-POSITIVE RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE^a

HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression	
See BINV-P 1 of 3 for general considerations for therapy selection for HR-positive, HER2-negative disease.	
First-Line Therapy	Second- and/or Subsequent-Line Therapy
Preferred First-Line Therapy • Aromatase inhibitor + CDK4/6 inhibitor^b ▶ Aromatase inhibitor + Ribociclib (category 1)^c ▶ Aromatase inhibitor + Abemaciclib ▶ Aromatase inhibitor + Palbociclib • For HER2-negative tumors with <i>PIK3CA</i> activating mutations: ▶ Fulvestrant/Inavolisib/Palbociclib, see BINV-Q 6 of 15 If disease progression on adjuvant endocrine therapy or relapse within 12 months of adjuvant endocrine therapy completion consider: → • Fulvestrant^d + CDK4/6 inhibitor^b ▶ Fulvestrant + Ribociclib (category 1)^e ▶ Fulvestrant + Abemaciclib (category 1)^e ▶ Fulvestrant + Palbociclib	Preferred Second- and/or Subsequent-Line Therapy • Fulvestrant + CDK4/6 inhibitor (Abemaciclib, Palbociclib, or Ribociclib) if CDK4/6 inhibitor not previously used (category 1)^{f,g} • For HER2-negative tumors with <i>PIK3CA</i> or <i>AKT1</i> activating mutations or <i>PTEN</i> inactivating mutations and genomic changes (eg, deletion), see BINV-Q 6 of 15^h • Everolimus + endocrine therapy (Exemestane, Fulvestrant, Tamoxifen)^{i,j} Useful in Certain Circumstances for Second- and/or Subsequent-Line Therapy • Megestrol acetate • Estradiol • Abemaciclib^l • Imlunestrant + Abemaciclib^m • Targeted therapy, see BINV-Q 7 of 15, and emerging biomarker options, see BINV-Q 8 of 15
Other Recommended for First- and/or Subsequent-Line Therapy • For HER2-negative and <i>ESR1</i> mutated tumors after a prior line of aromatase inhibitor ± CDK 4/6 inhibitor therapy (in adjuvant or metastatic setting), see BINV-Q 6 of 15 for options. • Fulvestrant + aromatase inhibitor (Anastrozole, Letrozole) (category 1)^k • Fulvestrant • Anastrozole • Letrozole • Tamoxifen • Exemestane	

[Footnotes on BINV-P 3 of 3](#)

evERA Study Design

A global, randomised, open-label, Phase III trial

Key Eligibility Criteria*

- ER+, HER2– aBC (1–3L of therapy)
- ≤ 2 prior lines of ET in the aBC setting
- PD or relapse during/post-CDK4/6i + ET
- No prior chemotherapy in the aBC setting
- Measurable disease per RECIST v1.1 or evaluable bone metastases

* Trial was enriched to 55% of patients with *ESR1*m at baseline (centrally tested via circulating tumour DNA)

Stratification Factors

- Prior treatment with fulvestrant (yes vs no)
- *ESR1*m (yes vs no/indeterminate)
- Site of disease (visceral [lung and/or liver involvement] vs non-visceral)

N = 373*

R
1:1

Enrolment period: August 2022 to October 2024

**Giredestrant (30 mg) +
everolimus (10 mg)[†]**

**SOC ET[‡] + everolimus (10 mg)[†]
[‡]Exemestane/fulvestrant/tamoxifen**

**Until PD
or
unacceptable
toxicity**

[†] Dexamethasone mouthwash prophylaxis and treatment was strongly recommended per SWISH trial protocol¹

Co-primary endpoints (RECIST v1.1)

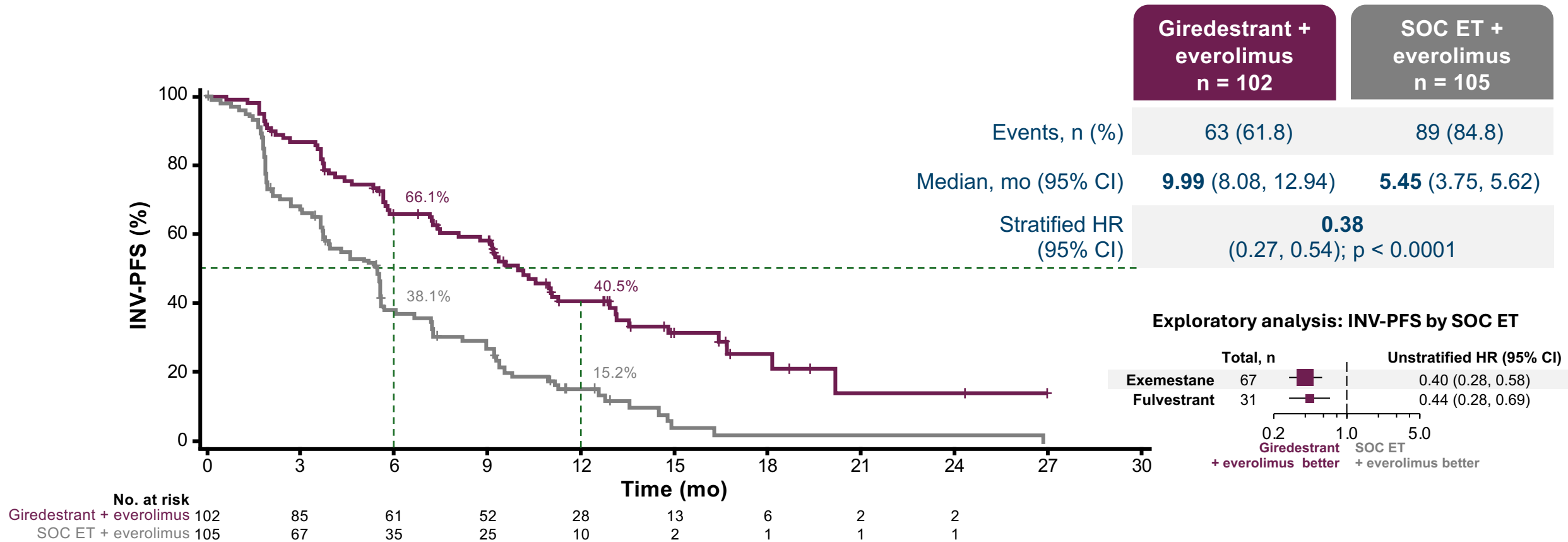
- INV-PFS in patients whose tumours had *ESR1*m
- INV-PFS in the ITT population

Key secondary endpoints

- OS
- INV-assessed ORR, DoR

ClinicalTrials.gov number, NCT05306340. Adapted from Mayer EL, *et al.* SABCS 2022 (poster OT2-01-07) with permission. 1–3L, first to third line; aBC, advanced breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DoR, duration of response; ER+, oestrogen receptor-positive; *ESR1*m, *ESR1* mutation; ET, endocrine therapy; HER2–, HER2-negative; INV, investigator-assessed; ITT, intention to treat; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; SOC ET, standard of care endocrine therapy.

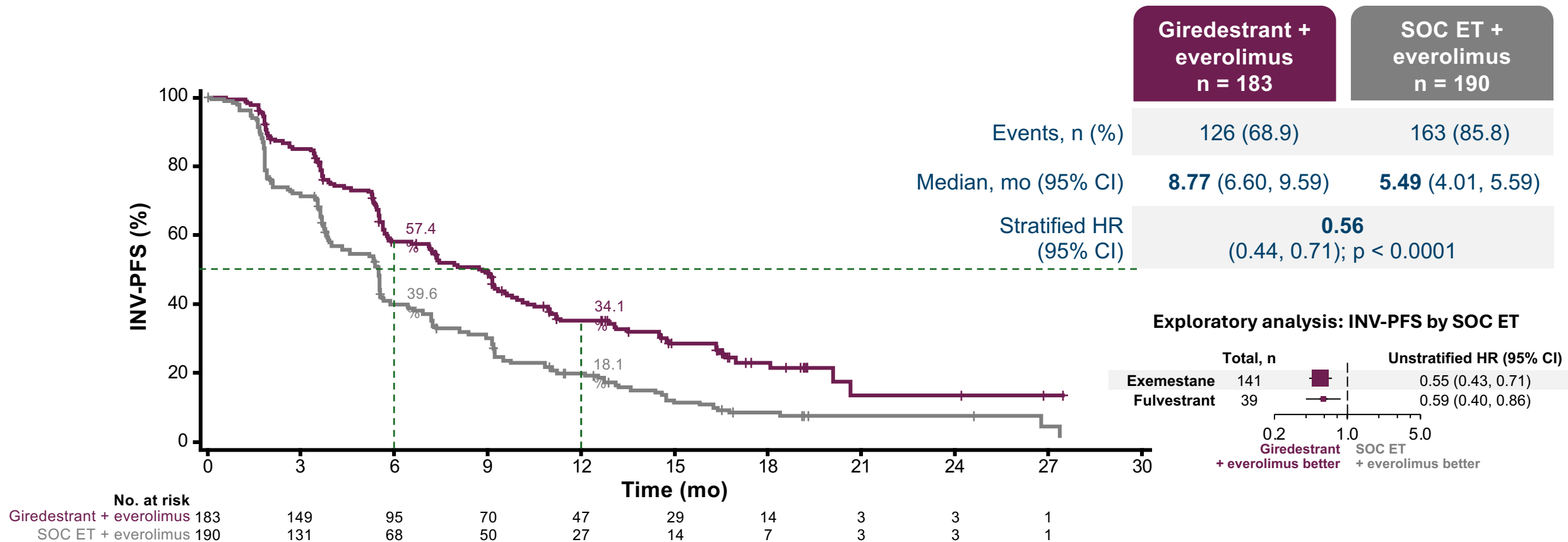
evERA: Co-primary Endpoint – INV-PFS in the *ESR1m* Population



Combination therapy with giredestrant + everolimus led to a clinically meaningful 62% reduction in the risk of progression or death in patients with *ESR1m*.

Data cutoff: 16 July 2025. PFS by blinded independent radiologist was similar to INV-PFS: Median PFS was 11.14 mo (giredestrant + everolimus) and 5.68 mo (SOC ET + everolimus); stratified HR, 0.49; 95% CI: 0.34, 0.71. CI, confidence interval; *ESR1m*, *ESR1* mutation; HR, hazard ratio; INV, investigator-assessed; mo, months; PFS, progression-free survival; SOC ET, standard of care endocrine therapy.

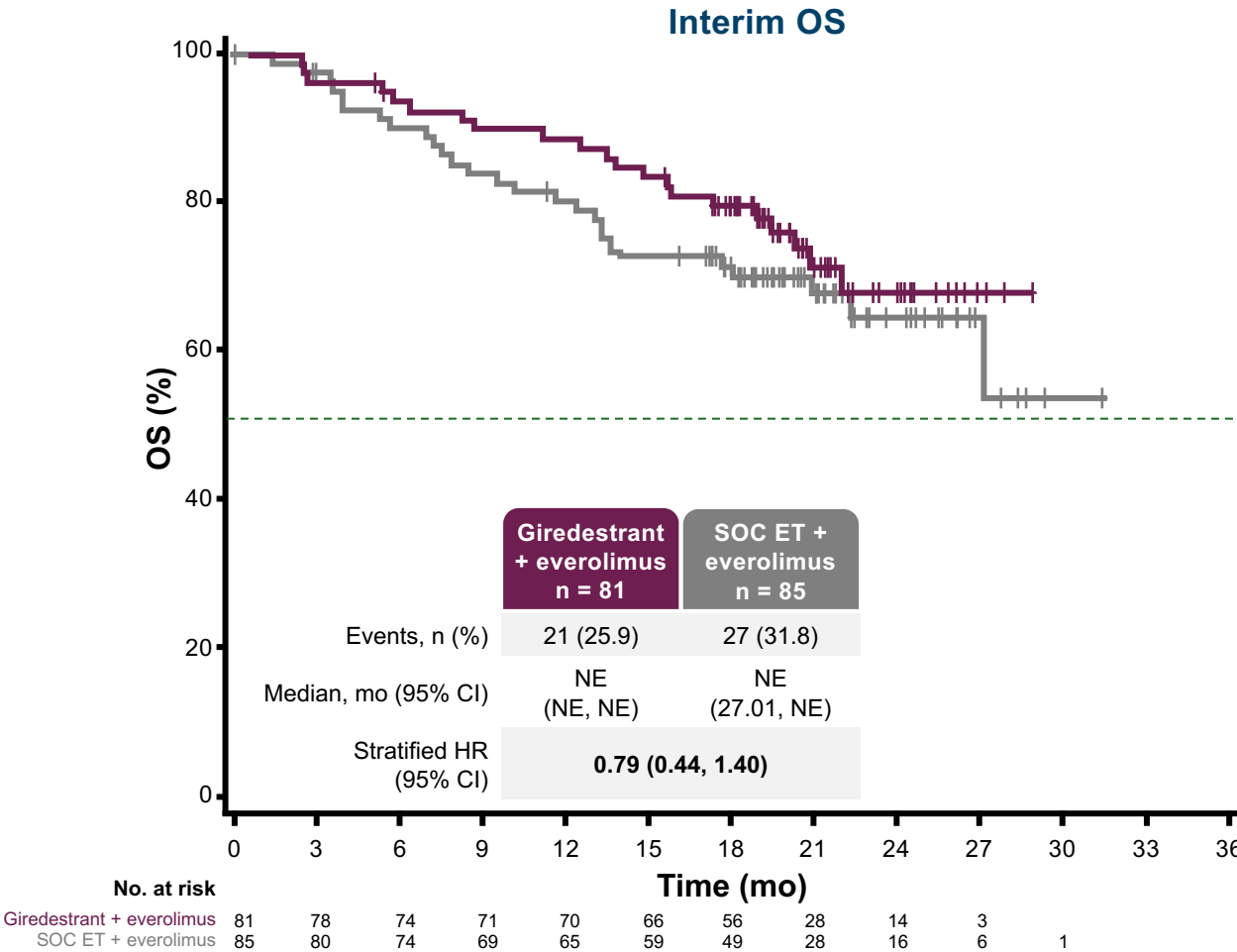
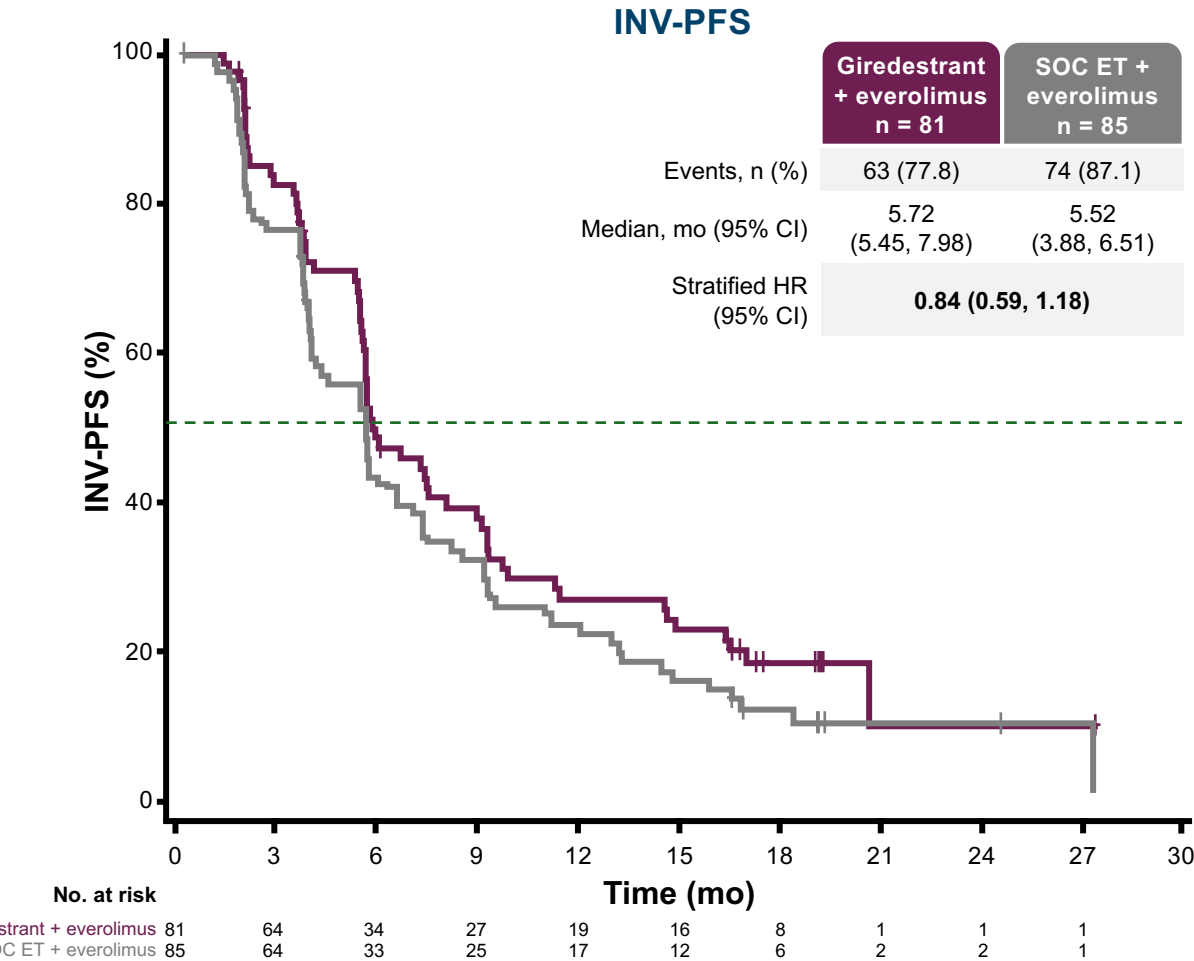
evERA: Co-primary Endpoint – INV-PFS in the ITT Population



Combination therapy with giredestrant + everolimus led to a clinically meaningful 44% reduction in the risk of progression or death in patients in the ITT population

Data cutoff: 16 July 2025. PFS by blinded independent radiologist was similar to INV-PFS: Median PFS was 10.32 mo (giredestrant + everolimus) and 7.26 mo (SOC ET + everolimus); stratified HR, 0.66; 95% CI: 0.50, 0.87. CI, confidence interval; HR, hazard ratio; INV, investigator-assessed; ITT, intention to treat; mo, months; PFS, progression-free survival; SOC ET, standard of care endocrine therapy.

evERA: INV-PFS and Interim OS in Patients Without *ESR1m* Detected (exploratory analysis)



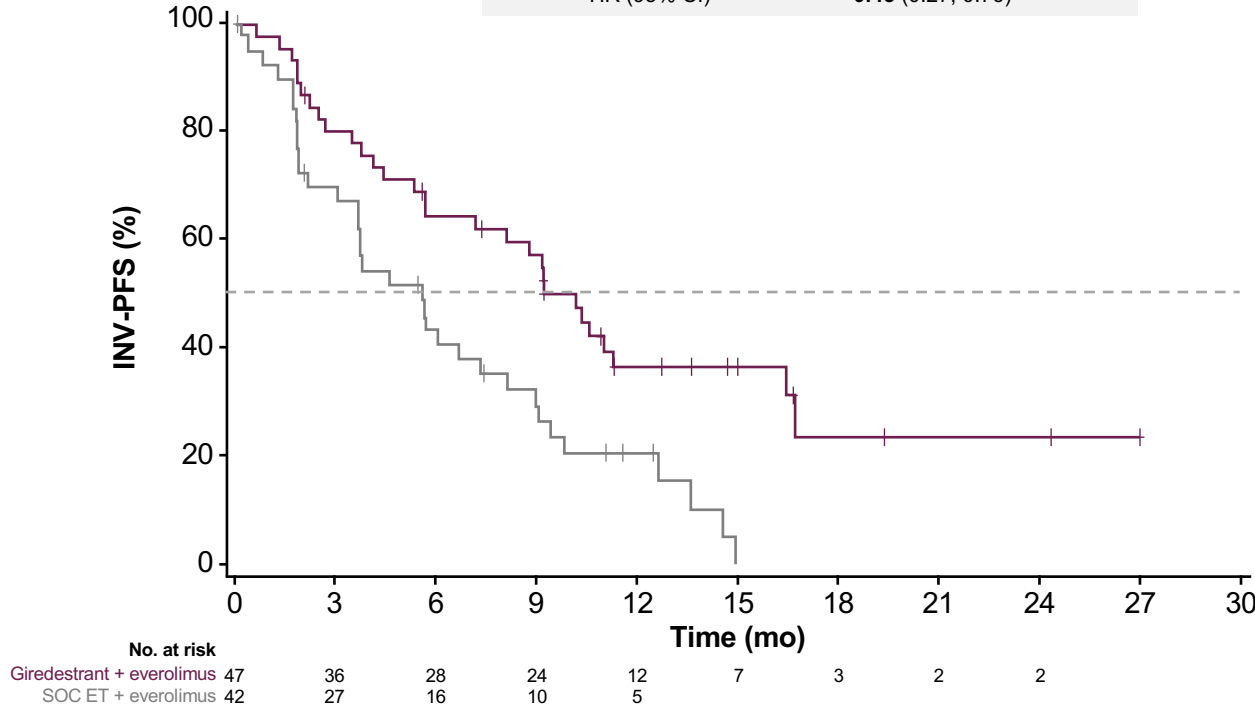
Data cutoff: 16 July 2025. CI, confidence interval; HR, hazard ratio; INV-PFS, investigator-assessed progression-free survival; mo, months; NE, not evaluable; OS, overall survival; SOC ET, standard of care endocrine therapy.

evERA: INV-PFS by *PIK3CA/AKT1/PTEN* Alteration Status

(*ESR1m* population)

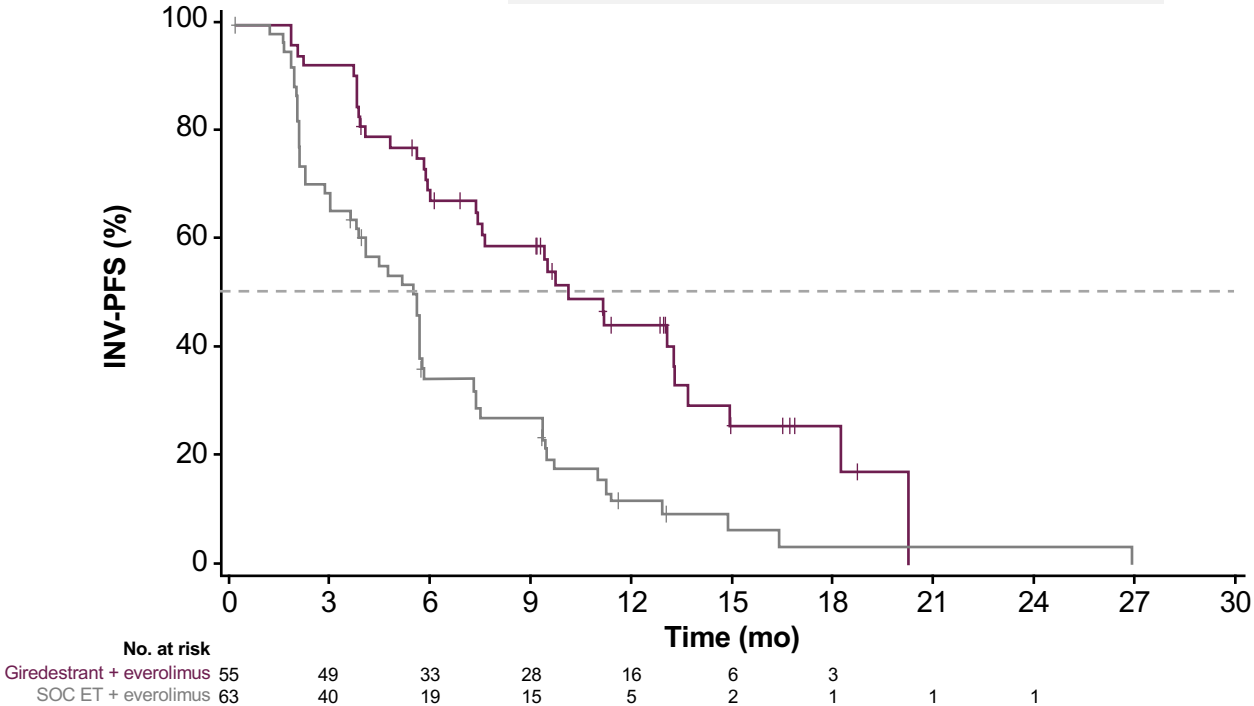
PIK3CA/AKT1/PTEN alteration detected

	Giredestrant + everolimus n = 47	SOC ET + everolimus n = 42
Events, n (%)	29 (61.7)	34 (81.0)
Median, mo (95% CI)	10.15 (7.16, 16.43)	5.55 (3.65, 8.11)
HR (95% CI)	0.45 (0.27, 0.76)	



PIK3CA/AKT1/PTEN alteration not detected

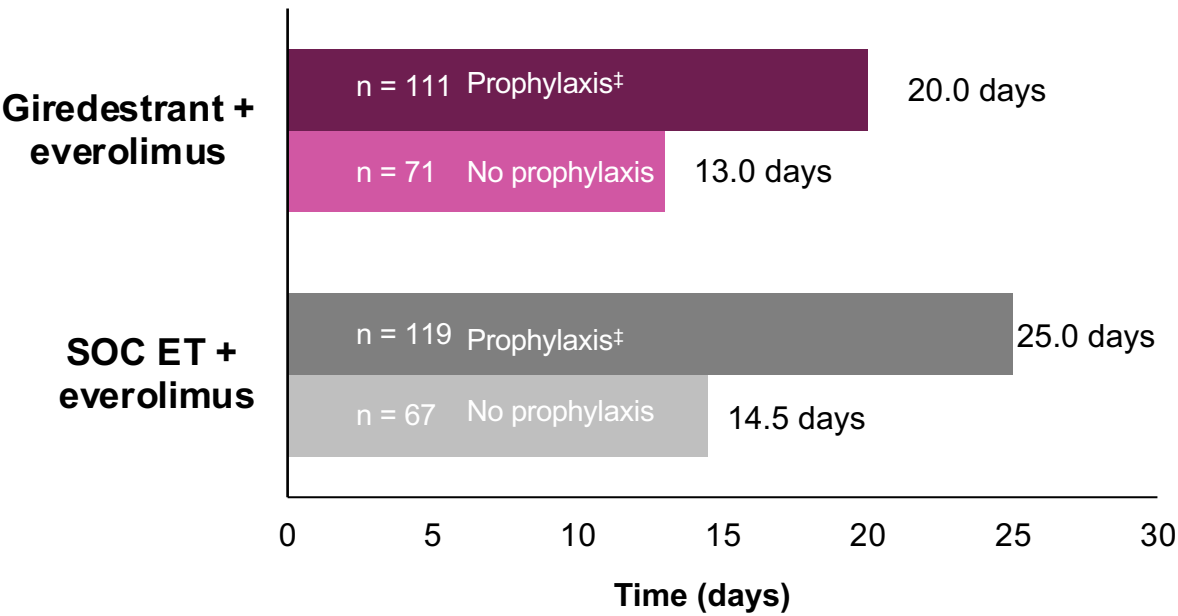
	Giredestrant + everolimus n = 55	SOC ET + everolimus n = 63
Events, n (%)	34 (61.8)	55 (87.3)
Median, mo (95% CI)	9.99 (7.26, 13.17)	5.45 (3.71, 5.59)
HR (95% CI)	0.41 (0.26, 0.63)	



Data cutoff: July 16, 2025. HR estimates are unstratified. AKT1, AKT serine/threonine kinase 1; CI, confidence interval; *ESR1m*, *ESR1* mutation; HR, hazard ratio; INV-PFS, investigator-assessed progression-free survival; mo, months; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog; SOC ET, standard-of-care endocrine therapy.

evERA: Stomatitis* Onset and Discontinuations

Median time to onset of stomatitis†



- 62.5% of patients received prophylaxis
 - 61.0% for giredestrant + everolimus
 - 64.0% for SOC ET + everolimus
- Prophylaxis delayed median onset of stomatitis

Treatment modifications due to stomatitis

Patients, n (%)	Treatment Group	
	Giredestrant + everolimus (n = 182)	SOC ET + everolimus (n = 186)
Dose interruption of any drug	5 (2.7)	6 (3.2)
Everolimus dose reduction	11 (6.0)	5 (2.7)
Everolimus discontinuation	2 (1.1)	0

Discontinuations of everolimus due to stomatitis were low

Data cut-off: 16 July 2025. * Medical concept. Includes the preferred terms, stomatitis, aphthous ulcer, mouth ulceration, glossodynia and glossitis. † No grade 4–5 stomatitis events were reported.
 ‡ Defined as steroid mouthwash used before the onset of stomatitis. SOC ET, standard-of-care endocrine therapy.

ELEVATE Phase I/II Trial Design

KEY ELIGIBILITY

- Women (pre-, peri-, or postmenopausal) or men
- ER+, HER2- a/mBC
- 1-2 lines of prior ET +/- CDK4/6i
- Prior fulvestrant allowed
- Primary endocrine resistance allowed
- No prior chemotherapy in the a/mBC setting
- ≥1 measurable lesion as per RECIST v1.1 or a mainly lytic bone lesion

ELEVATE PHASE 1b (n=90)

Elacestrant 86-345 mg* combined with either:

Alpelisib 150-250 mg^{a,b,c}
Everolimus 5-10 mg^{d,e,f,g}
Palbociclib 100-125 mg^{h,i,j}
Ribociclib 400-600 mg^{k,l,m,n,o}
Capivasertib 320-400 mg^{p,q,r}

ELECTRA PHASE 1b (n=27)

Elacestrant 258-345 mg* combined with **Abemaciclib** 100-150 mg^{s,t,i}

RP2D

ELEVATE PHASE 2

Elacestrant 345 mg + Everolimus 7.5 mg (n=50)

Elacestrant 345 mg + Abemaciclib 150 mg (n=60)

Elacestrant 345 mg + Ribociclib 400 mg (n=30)

Elacestrant 345 mg + Capivasertib 320 mg (n=60)

Phase 2 Objectives

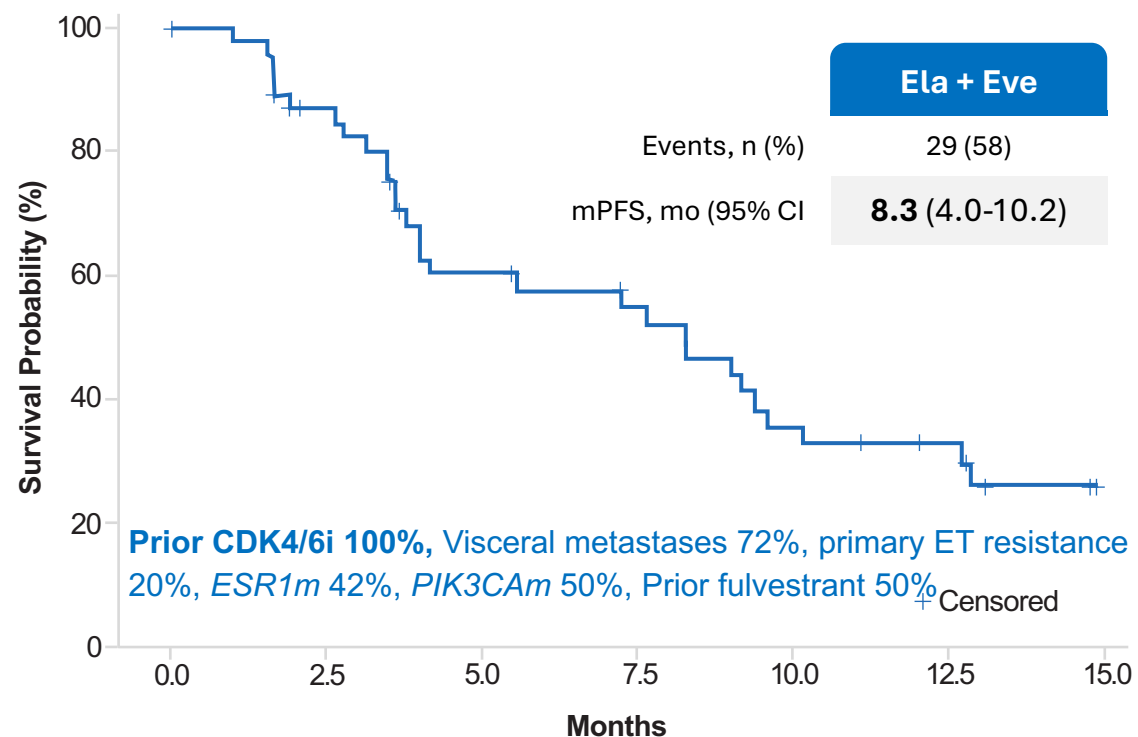
Primary: PFS (RECIST v1.1)

Secondary: ORR, DoR, CBR, PFS, OS, and safety

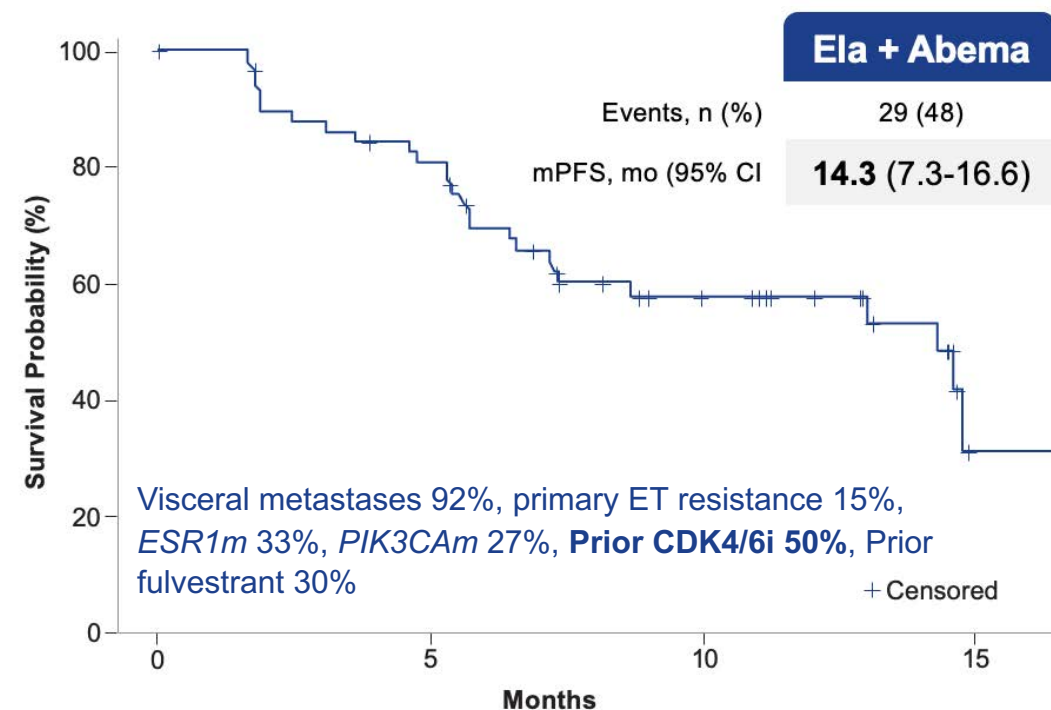
*Elacestrant and everolimus dose are administered QD.
 Abemaciclib is administered BID.*

Elacestrant 86 mg is equivalent to 100 mg elacestrant hydrochloride; elacestrant 172 mg is equivalent to 200 mg elacestrant hydrochloride; elacestrant 258 mg is equivalent to 300 mg elacestrant hydrochloride; elacestrant 345 mg is equivalent to 400 mg elacestrant hydrochloride. ^aElacestrant 258 mg + alpelisib 250 mg (cohort 1); ^bElacestrant 258 mg* + alpelisib 200 mg (cohort -1); ^cElacestrant 258 mg* + alpelisib 150 mg (cohort -2); ^dElacestrant 258 mg* + everolimus 5 mg (cohort 1); ^eElacestrant 345 mg* + everolimus 5 mg (cohort 2); ^fElacestrant 345 mg* + everolimus 10 mg (cohort 3); ^gElacestrant 345 mg* + everolimus 7.5 mg (cohort 4); ^hElacestrant 258 mg* + palbociclib 100 mg (cohort 1); ⁱElacestrant 345 mg* + palbociclib 100 mg (cohort 2); ^jElacestrant 345 mg* + palbociclib 125 mg (cohort 3); ^kElacestrant 86 mg* + ribociclib 400 mg (cohort 1); ^lElacestrant 172 mg* + ribociclib 400 mg (cohort 2); ^mElacestrant 258 mg* + ribociclib 400 mg (cohort 3); ⁿElacestrant 172 mg* + ribociclib 600 mg (cohort 4); ^oElacestrant 345 mg* + ribociclib 400 mg (cohort 5); ^pElacestrant 258 mg* + capivasertib 320 mg (cohort 1); ^qElacestrant 345 mg* + capivasertib 320 mg (cohort 2); ^rElacestrant 345 mg* + capivasertib 400 mg (cohort 3); ^sElacestrant 258 mg* + abemaciclib 100 mg (cohort 1); ^tElacestrant 345 mg* + abemaciclib 100 mg (cohort 2); ⁱElacestrant 345 mg* + abemaciclib 150 mg (cohort 3). a/mBC, advanced or metastatic breast cancer; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DoR, duration of response; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; n, number; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; v, version.

ELEVATE: PFS Elacestrant + Everolimus or Elacestrant + Abemaciclib



Ela + Eve showed 82.9% DCR, 19.5% ORR, 8.54 mos mDOR



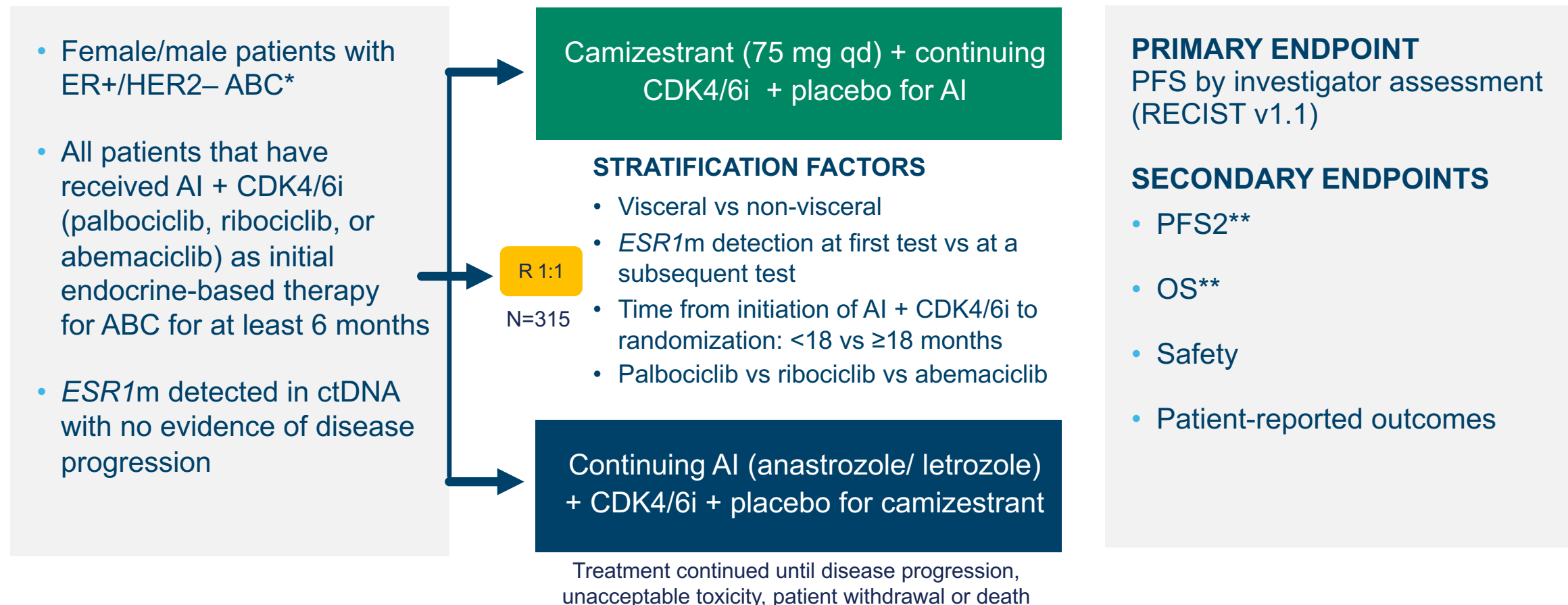
Ela + Abema showed 91.2% DCR, 24.6% ORR, 14.75 mos mDOR

Elacestrant + everolimus or elacestrant + abemaciclib combinations showed a consistent PFS benefit across all subgroups

Data cut-off: Sept 15, 2025. CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; Ela, elacestrant; ESR1m, estrogen receptor 1 mutation; ET, endocrine therapy; Eve, everolimus; mo, months; mPFS, median progression-free survival; n, number; NR, not reached; PIK3CAm, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha mutation; PFS, progression-free survival; wt, wild-type. DCR Disease Control Rate, ORR Overall Response Rate, mDOR Median Duration of Response

SERENA-6: Step 2 Study Design

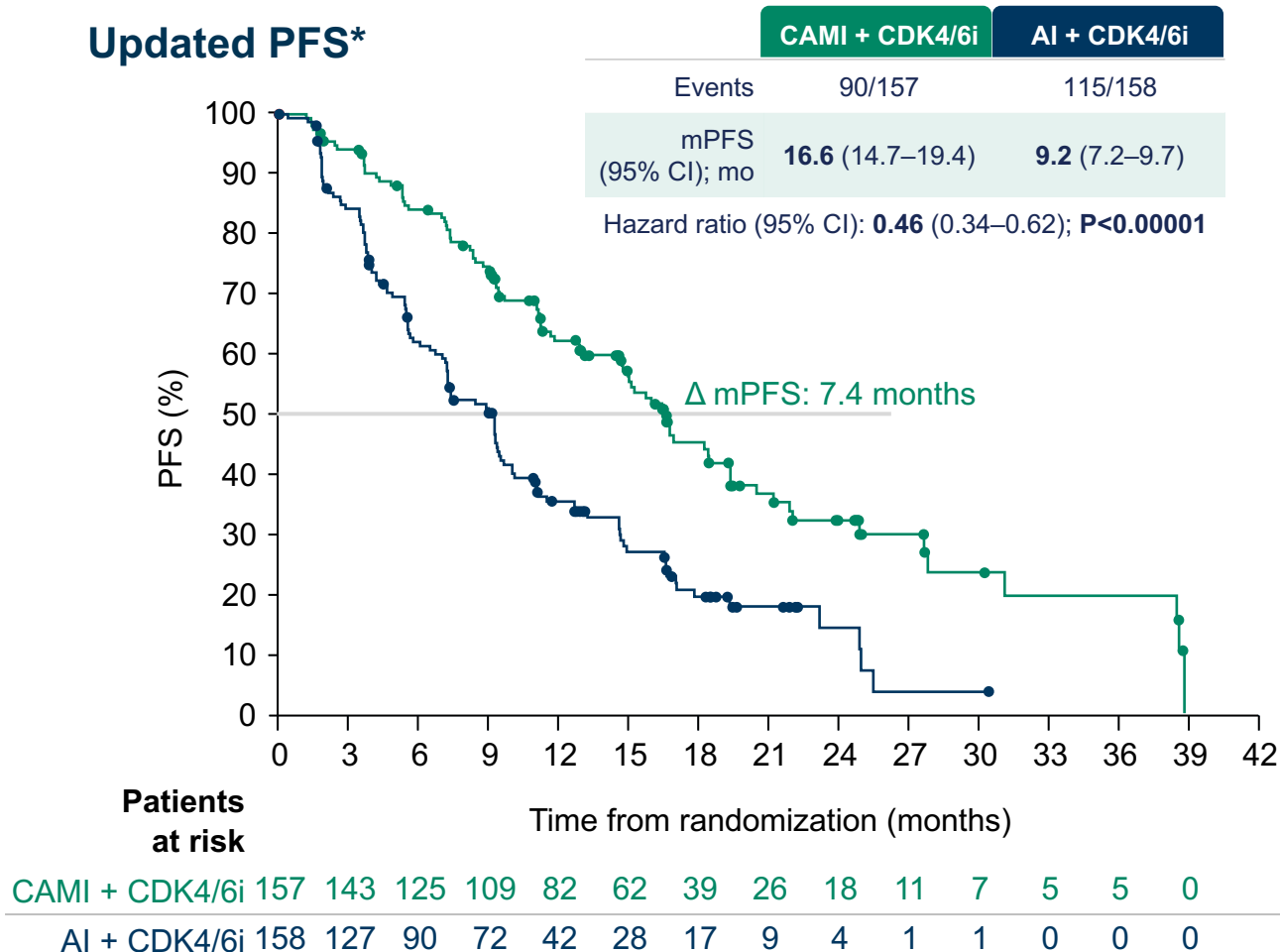
Phase III, randomized, double-blind, placebo-controlled study (NCT04964934)



*Pre- or perimenopausal women, and men received a luteinizing hormone–releasing hormone agonist per clinical guidelines. **Key secondary endpoint. OS, overall survival; PFS2, second progression-free survival; qd, once daily dose; R, randomized; RECIST, response evaluation criteria in solid tumors.

SERENA-6: Switching to Camizestrant + CDK4/6i Prolongs Time to Progression and Time to First Subsequent Therapy

Updated PFS*



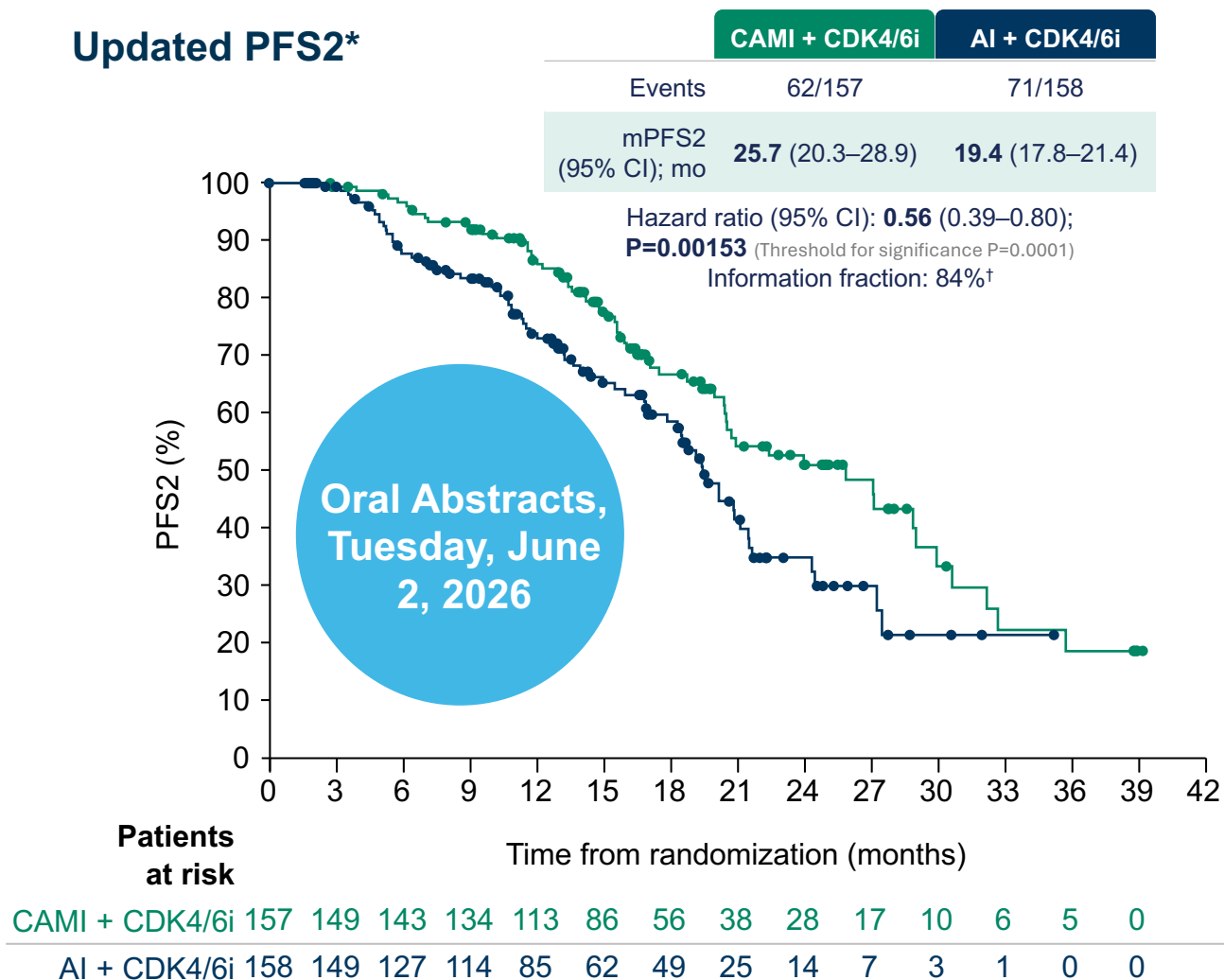
Switching to camizestrant + CDK4/6i treatment led to a clinically meaningful improvement in PFS compared with continuing AI + CDK4/6i

- The **time to first subsequent therapy** (defined as the time from randomization to receiving a first subsequent therapy, or death) also favored the camizestrant + CDK4/6i arm compared with the AI + CDK4/6i arm; **hazard ratio (95% CI): 0.47 (0.35–0.62)**
- The magnitude of benefit in time to first subsequent therapy was **consistent with PFS**

CAMI, camizestrant; mo, months; CI, confidence interval; DCO2, data cutoff 2; mPFS, median PFS; TFST, time to first subsequent therapy; RECIST, Response Evaluation Criteria in Solid Tumors. *Second pre-specified data cut **DCO2: June 30, 2025**. At DCO2, 58 patients in the camizestrant + CDK4/6i arm and 23 patients in the AI + CDK4/6i arm were still receiving study treatments. There were 88/157 TFST events in the camizestrant + CDK4/6i arm and 117/158 in the AI + CDK4/6i arm. PFS was defined per RECIST v1.1. The PFS and TFST hazard ratio and 95% CI are estimated using a Cox proportional hazards model stratified by disease site, ESR1m status detectable at first versus subsequent ctDNA tests, and time from initiation of AI + CDK4/6i to randomization.

SERENA-6: Switching to Camizestrant + CDK4/6i Prolongs Time To Second Progression And Time To Second Subsequent Therapy

Updated PFS2*



Switching to camizestrant + CDK4/6i treatment led to a clinically meaningful prolongation in PFS2 compared with continuing AI + CDK4/6i, demonstrating that the PFS gain is maintained in the subsequent line of therapy

- The **time to second subsequent therapy** (defined as the time from randomization to receiving a second subsequent therapy, or death) also favored the camizestrant + CDK4/6i arm compared with the AI + CDK4/6i arm; **hazard ratio (95% CI): 0.57 (0.40–0.81)**
- The magnitude of benefit in time to second subsequent therapy was **consistent with PFS2**

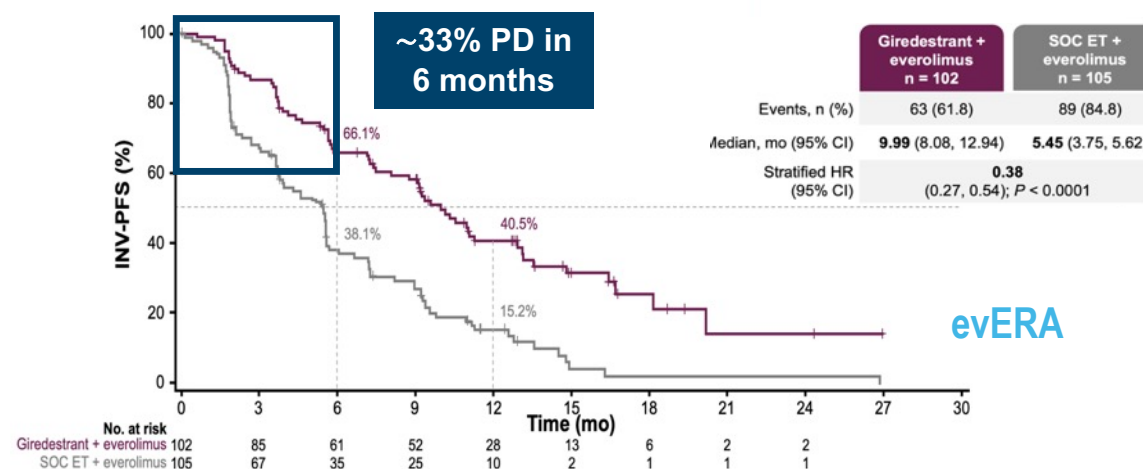
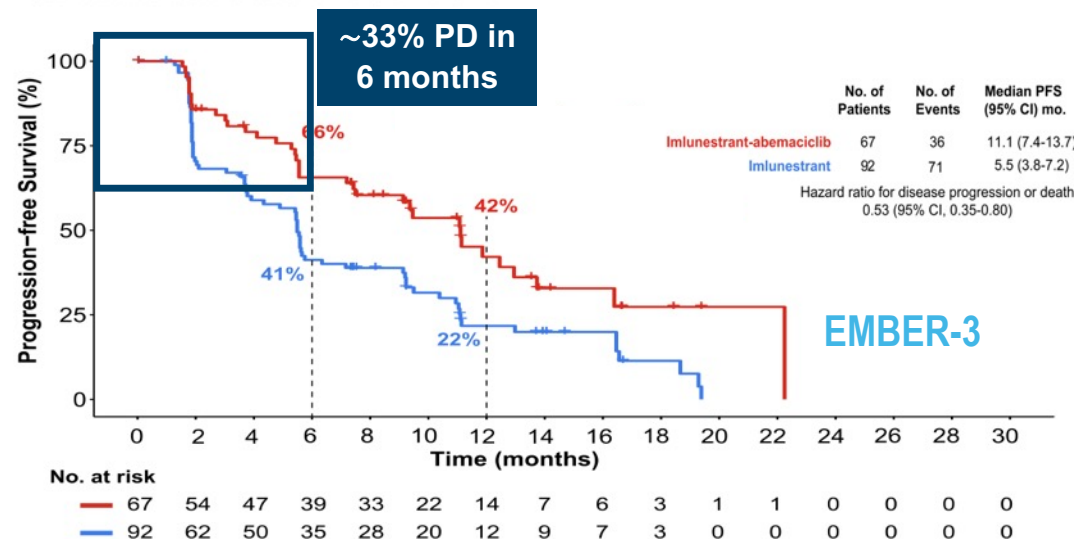
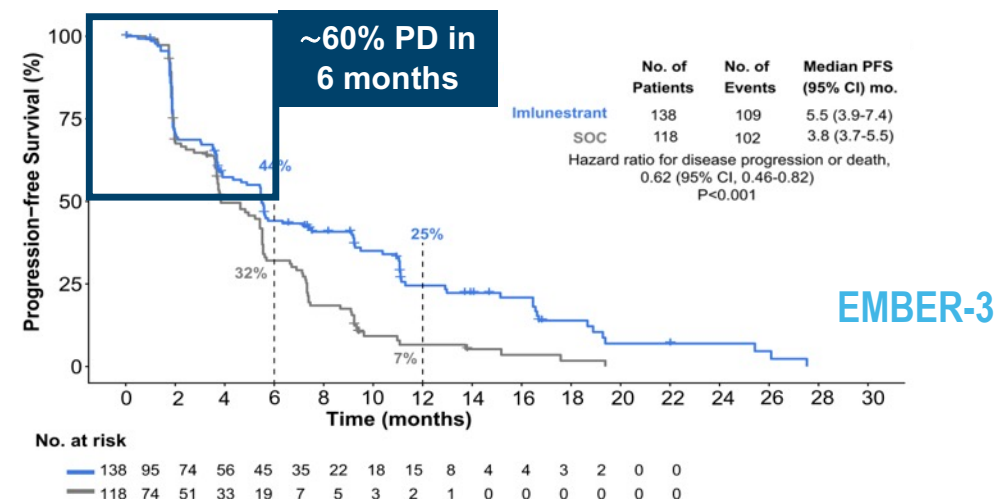
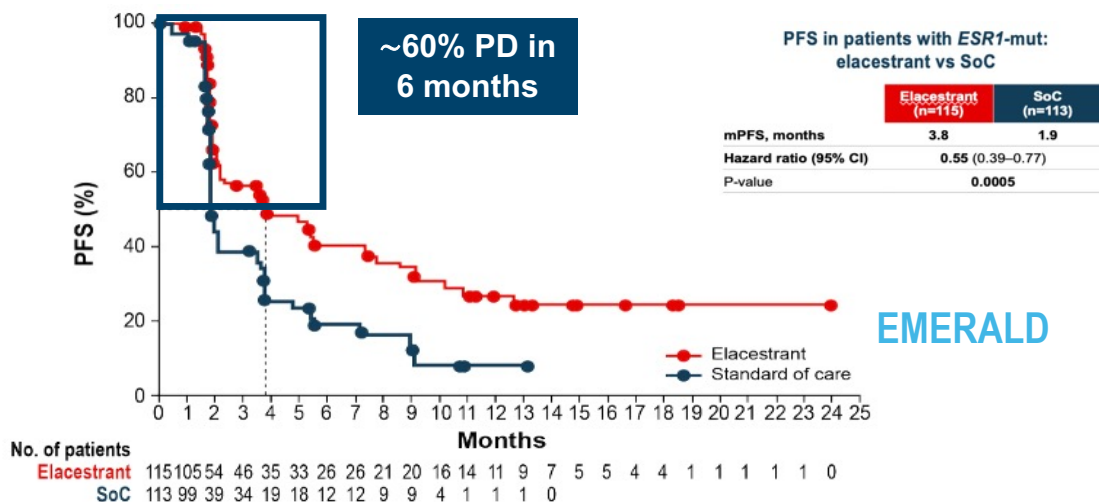
(m)PFS2, (median) PFS2; TSST, time to second subsequent therapy.

*Second pre-specified data cut DCO2: June 30, 2025. †Information fraction: the number of PFS2 events at this interim analysis divided by the number of PFS2 events expected at final analysis, multiplied by 100.

There were 60/157 TSST events in the camizestrant + CDK4/6i arm and 77/158 in the AI + CDK4/6i arm. The PFS2 and TSST hazard ratio and 95% CI are estimated using a stratified Cox proportional hazards model stratified by *ESR1m* detectable at first versus subsequent ctDNA tests and time from initiation of AI + CDK4/6i to randomization.

SERD Combination is Superior to Monotherapy

Early progression in *ESR1* mut: single agent SERD vs SERD + targeted therapy



Conclusions

Oral SERD combinations  **co-target** resistance pathways and can **improve efficacy** over SERD monotherapy in the pretreated setting

 **Excellent tolerability** of oral SERDs has allowed **safe combinations** with targeted agents including CDK4/6i, mTOR, PIK3CA inhibitors

 **Await first FDA approval** for an oral SERD combination option in pretreated patients

 **Role of oral SERD combinations in 1L** or early-stage setting, with less prevalence of ESR1 mutations, remains less clear

Regulatory and reimbursement issues aside, which treatment would you likely recommend for a 65-year-old woman (PS 0) with ER/PR-positive, HER2-low (IHC 1+) mBC who experiences PD after receiving ribociclib/letrozole for 2 years?

Her biomarker testing results are:

- **PIK3CA/AKT/PTEN-negative**
- **ESR1-positive**
- **BRCA wild type**

Age 65, PS 0; HER2 IHC 1+, BRCA wild-type mBC
Received ribociclib/letrozole for 2 years
PIK3CA/AKT1/PTEN-negative, ESR1-positive

		Multiple minimally symptomatic bone metastases	Multiple symptomatic visceral metastases and normal LFTs
	Dr Hurvitz	Giredestrant + everolimus	Giredestrant + everolimus
	Dr Mayer	Giredestrant + everolimus or imlunestrant + abemaciclib	Giredestrant + everolimus or imlunestrant + abemaciclib
	Dr O'Shaughnessy	Elacestrant	Imlunestrant + abemaciclib
	Dr Tolaney	Elacestrant	Giredestrant + everolimus or imlunestrant + abemaciclib
	Dr Turner	Giredestrant + everolimus	Giredestrant + everolimus
	Dr Kaklamani	Elacestrant	Elacestrant

How would you indirectly compare the global efficacy of imlunestrant/abemaciclib to that of giredestrant/everolimus for endocrine therapy-pretreated, HR-positive, HER2-negative mBC that is ...?

		ESR1 mutant	ESR1 wild type
	Dr Hurvitz	About the same	About the same
	Dr Mayer	About the same	About the same
	Dr O'Shaughnessy	About the same	Imlunestrant/abemaciclib is more efficacious
	Dr Tolaney	About the same	About the same
	Dr Turner	Giredestrant/everolimus is more efficacious	About the same
	Dr Kaklamani	About the same	Imlunestrant/abemaciclib is more efficacious

If imlunestrant/abemaciclib were available today, for which types of patients with HR-positive, HER2-negative mBC would you most likely employ it?



Dr Hurvitz

**ESR1+ after palbociclib- or ribociclib-based therapy
if giredestrant/everolimus is not available**



Dr Mayer

ESR1 mutant where I do not want to use oral SERD monotherapy



Dr O'Shaughnessy

**Pts with ESR1-mutant disease in the first- or second-line that is CDK4/6
inhibitor-naïve or pretreated with palbociclib or ribociclib + AI**



Dr Tolaney

**ESR1m in the second line after progression
on AI + palbociclib or ribociclib**



Dr Turner

None, I would use giredestrant + everolimus instead



Dr Kaklamani

ESR1 wild-type after progression on CDK4/6

If giredestrant/everolimus were available today, for which types of patients with HR-positive, HER2-negative mBC would you most likely employ it?



Dr Hurvitz

Post-CDK4/6 inhibitor, ESR1 mutant



Dr Mayer

ESR1 mutant where I do not want to use oral SERD monotherapy



Dr O'Shaughnessy

Pts with ESR1-mutant ET-sensitive disease after progression on AI + CDK4/6 inhibitor



Dr Tolaney

ESR1m in the second line after progression on AI + CDK4/6 inhibitor with visceral metastases



Dr Turner

Second line ESR1 mutant



Dr Kaklamani

Second line for most patients

Agenda

Module 1: Current and Future Roles of Agents Targeting the PI3K/AKT/mTOR Pathway and Oral SERDs in First-Line Therapy for HR-Positive, HER2-Negative Metastatic Breast Cancer (mBC) — Dr Turner

Module 2: Role of Oral SERD Monotherapy in the Treatment of Progressive HR-Positive, HER2-Negative mBC — Dr O'Shaughnessy

Module 3: Potential Use of Oral SERD-Containing Combination Regimens in Managing Progressive HR-Positive, HER2-Negative mBC — Dr Mayer

Module 4: Clinical Utility of Agents Targeting the PI3K/AKT/mTOR Pathway for Patients with Progressive HR-Positive, HER2-Negative mBC — Dr Hurvitz

Module 5: Potential Use of Oral SERDs for HR-Positive, HER2-Negative Localized BC — Dr Tolaney

Clinical Utility of Agents Targeting the PI3K/AKT/mTOR Pathway for Patients with Progressive HR-Positive, HER2-Negative MBC

Sara A. Hurvitz, MD, FACP

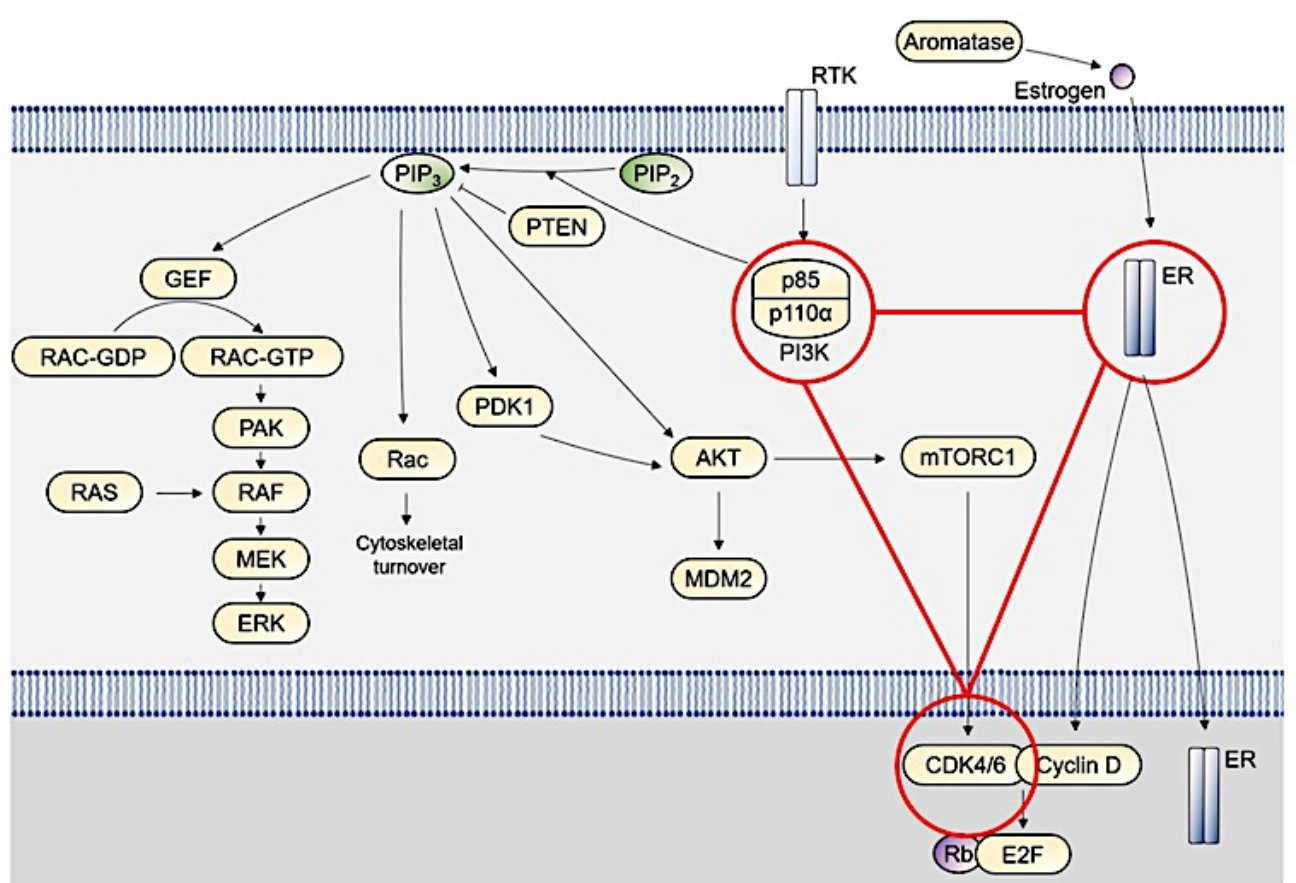
Professor of Medicine

Smith Family Endowed Chair in Women's Health

Head, Division of Hematology/Oncology, University of Washington School of Medicine

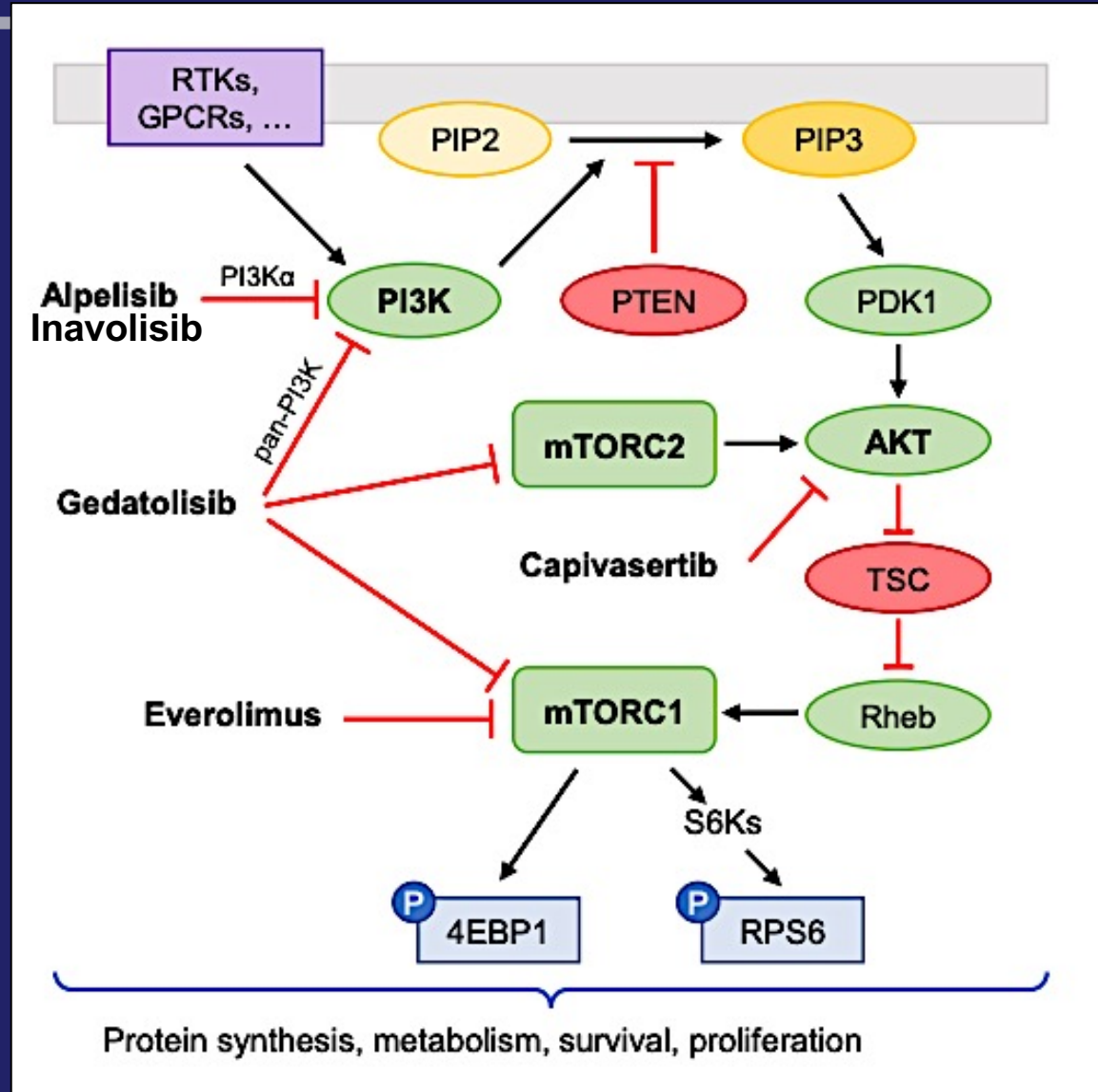
Senior Vice President, Clinical Research Division, Fred Hutchinson Cancer Center

PIK3CA-Mutated, HR+, HER2- MBC



- Up to 70% of breast cancers have a molecular aberration of PI3K/AKT/mTOR pathway
- PIK3CA* mutations (*PIK3CAm*) occur in ~ 40% of HR+, HER2- breast cancers
- Baseline PI3K activation associated with poor prognosis after adjuvant ET**

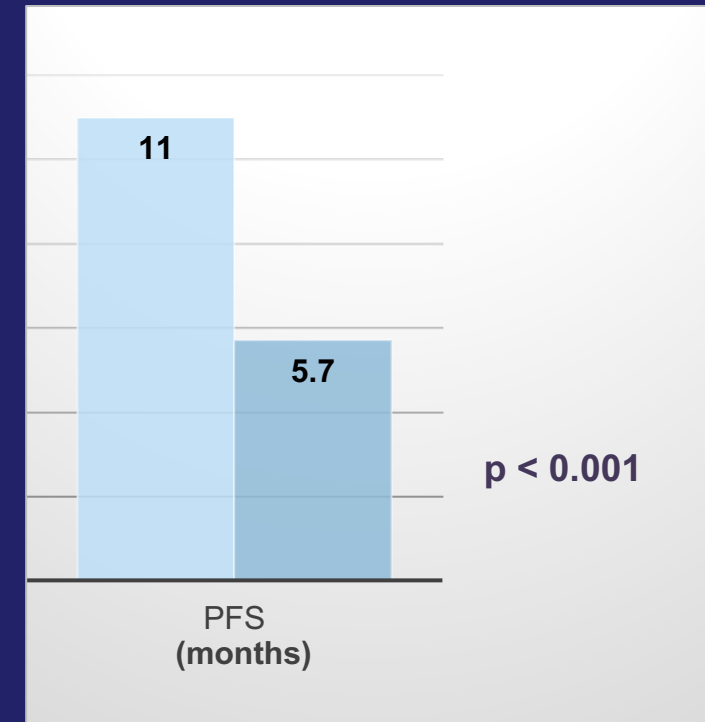
Mechanism of Action of 5 PI3K Pathway Inhibitors



Phase III Data for targeting *PIK3CA* mutated breast cancer in endocrine-resistant disease

SOLAR-1 Trial Phase III Trial: *PIK3CA* inhibitor + SERD

- N=572, postmenopausal women who previously received endocrine therapy with *PIK3CA*-mutated HR+/HER2- mBC
- Treatment*
 - Alpelisib 300 mg PO daily + fulvestrant 500 mg IM every 28 days
 - Placebo + fulvestrant
- Results
 - Overall response 26.6% vs. 12.8%
 - Grade ≥ 3 AE: hyperglycemia 36.6%, rash 10%, diarrhea 6.7%



CAPItello-291: Study overview

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

Patients with HR+/HER2– ABC

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

R1:1
(N=708)

Capivasertib

400 mg twice daily,
4 days on, 3 days off

Fulvestrant

500 mg: cycle 1, days 1 &
15; then every 4 weeks

Stratification factors:

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

Placebo

Twice daily,
4 days on, 3 days off

Fulvestrant

500 mg: cycle 1, days 1 &
15; then every 4 weeks

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

2/3 had prior CDK4/6i; 40% had PI3K-pathway alteration

HER2– was defined as IHC 0 or 1+, or IHC 2+/ISH–. *Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia.

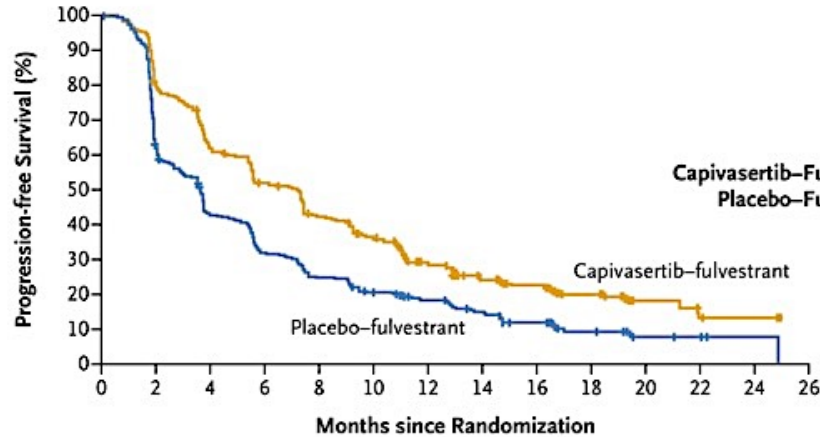
ABC, advanced (locally advanced [inoperable] or metastatic) breast cancer.

Pre- or peri-menopausal women also received a luteinizing hormone-releasing hormone agonist for the duration of the study treatment

**Turner NC et al. N Engl J Med
2023;388:2058-2070**

CAPItello-291: Fulvestrant + Capivasertib or Placebo

A Overall Population



	No. of Patients	No. of Events	Median Progression-free Survival (95% CI) mo
Capiasertib-Fulvestrant	355	258	7.2 (5.5–7.4)
Placebo-Fulvestrant	353	293	3.6 (2.8–3.7)

Adjusted hazard ratio for disease progression or death, 0.60 (95% CI, 0.51–0.71)
P<0.001

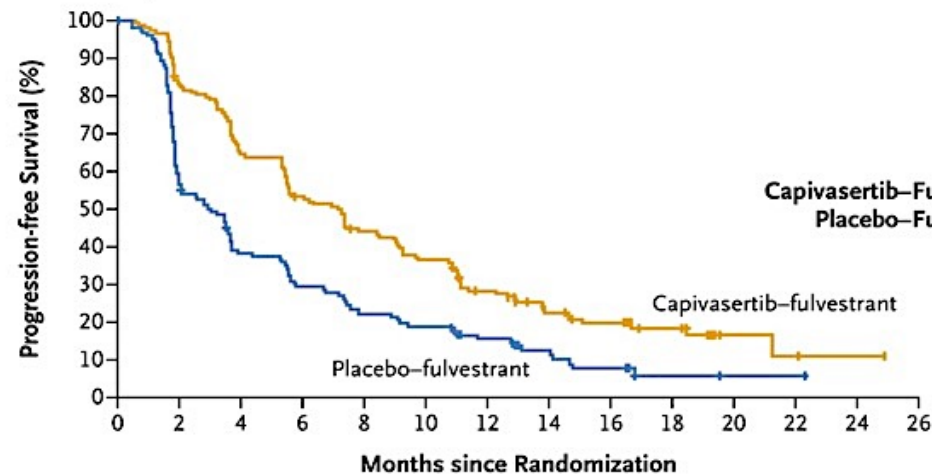
No. at Risk

Capiasertib-fulvestrant	355	266	207	172	138	115	78	55	43	25	8	5	2	0
Placebo-fulvestrant	353	207	142	106	83	66	51	33	23	11	4	3	1	0

FDA approved 11/2023:
-HR+/HER2- with PIK3CA, AKT1 and/or PTEN-alteration after PD on ≥ 1 endocrine therapy in MBC (or ≤ 12 mos from adjuvant ET)

- ~70% prior CDK4/6i
- ~18% prior chemo for MBC
- Overall survival not statistically significantly different

B Patients with AKT Pathway-Altered Tumors



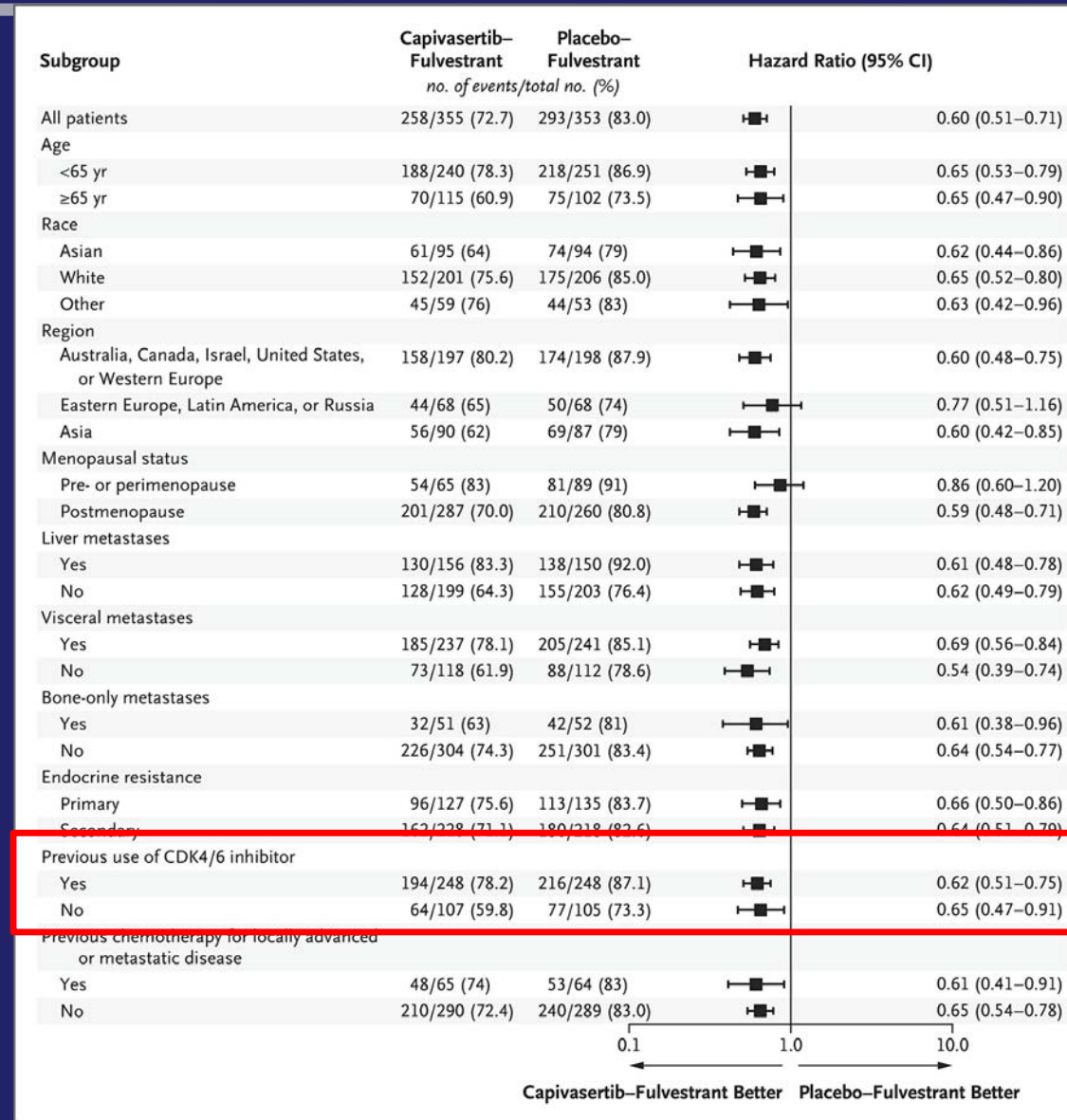
	No. of Patients	No. of Events	Median Progression-free Survival (95% CI) mo
Capiasertib-Fulvestrant	155	121	7.3 (5.5–9.0)
Placebo-Fulvestrant	134	115	3.1 (2.0–3.7)

Adjusted hazard ratio for disease progression or death, 0.50 (95% CI, 0.38–0.65)
P<0.001

No. at Risk

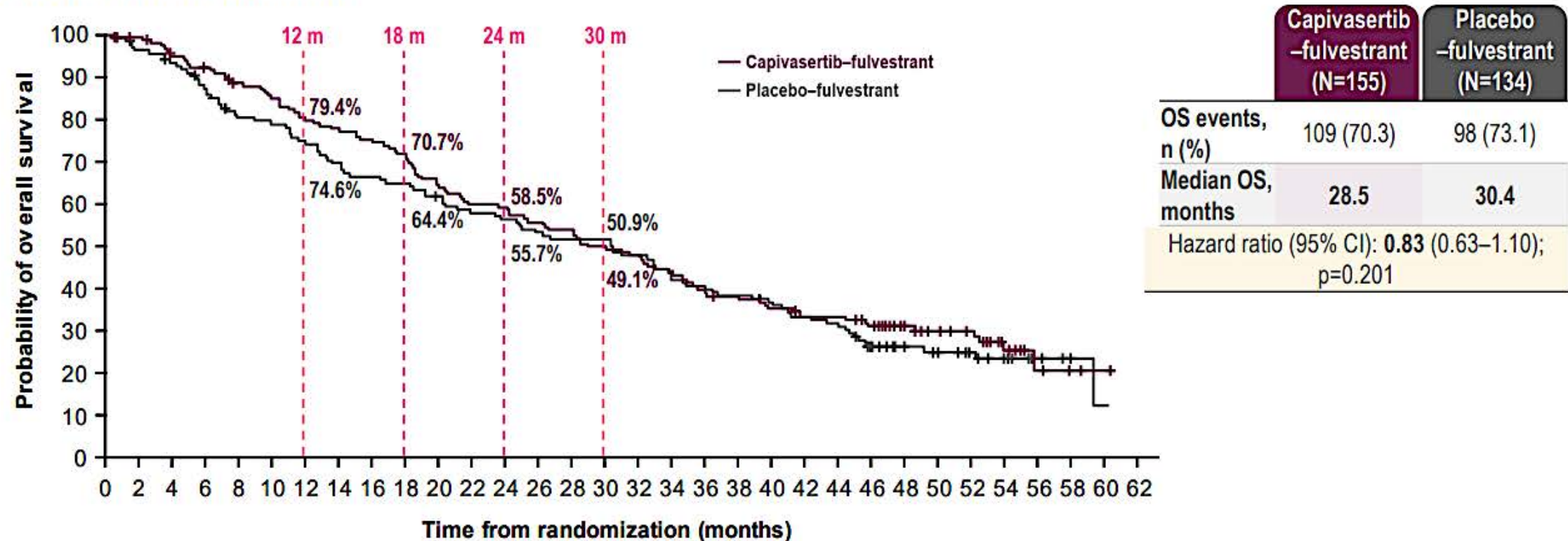
Capiasertib-fulvestrant	155	127	99	80	65	54	38	26	21	12	3	2	1	0
Placebo-fulvestrant	134	77	48	37	28	24	17	11	6	2	1	1	0	0

Capivasertib Benefit Seen After CDK4/6i



Key secondary endpoint: OS (altered population)

There was a numerical trend in hazard ratio favouring capivasertib–fulvestrant vs placebo–fulvestrant for the *PIK3CA*/*AKT1*/*PTEN*-altered population, but the analysis was underpowered and statistical significance was not reached



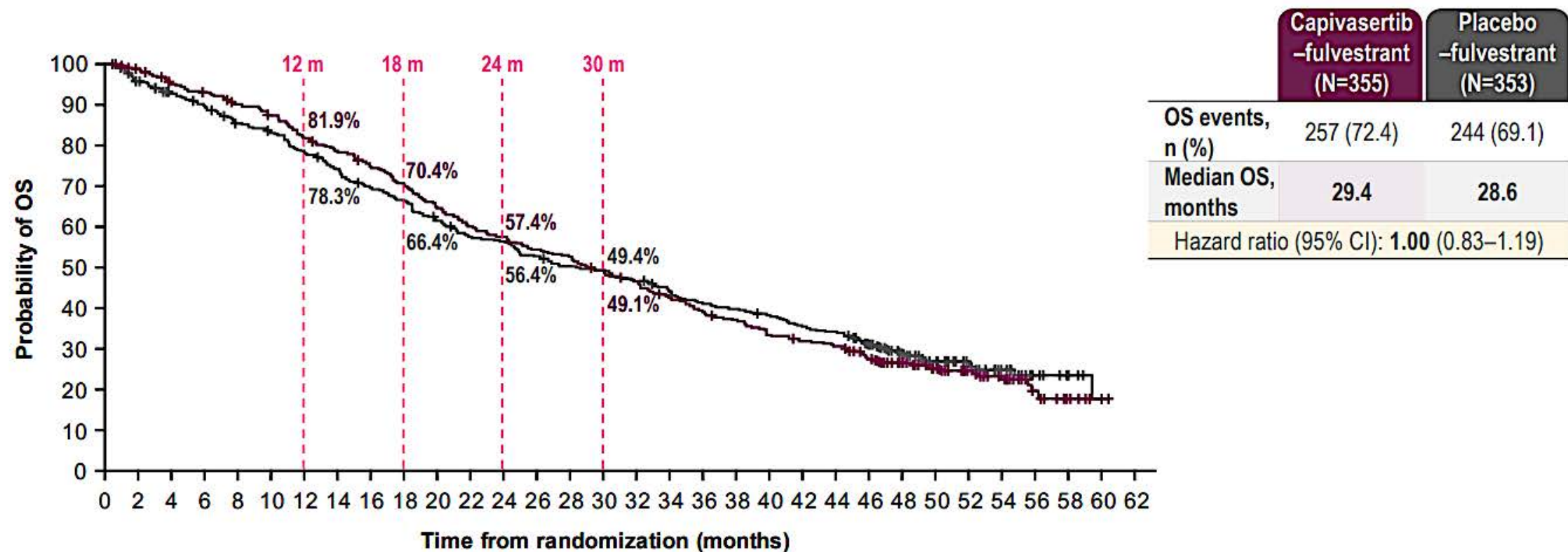
Number of patients at risk

Capivasertib–fulvestrant	155	153	144	139	131	126	118	115	111	105	94	88	87	82	79	73	70	64	57	54	50	46	46	41	33	26	21	13	4	2	1	0
Placebo–fulvestrant	134	127	122	113	102	100	95	88	84	82	77	72	70	66	64	64	59	52	49	47	44	40	38	27	21	18	14	10	5	2	1	0

Final DCO: 16 June 2025. Data maturity: 71.6%.

Key secondary endpoint: OS (overall population)

As statistical significance was not observed in the altered population, OS was not formally tested in the overall population; no numerical difference in the risk of death was observed between treatment arms



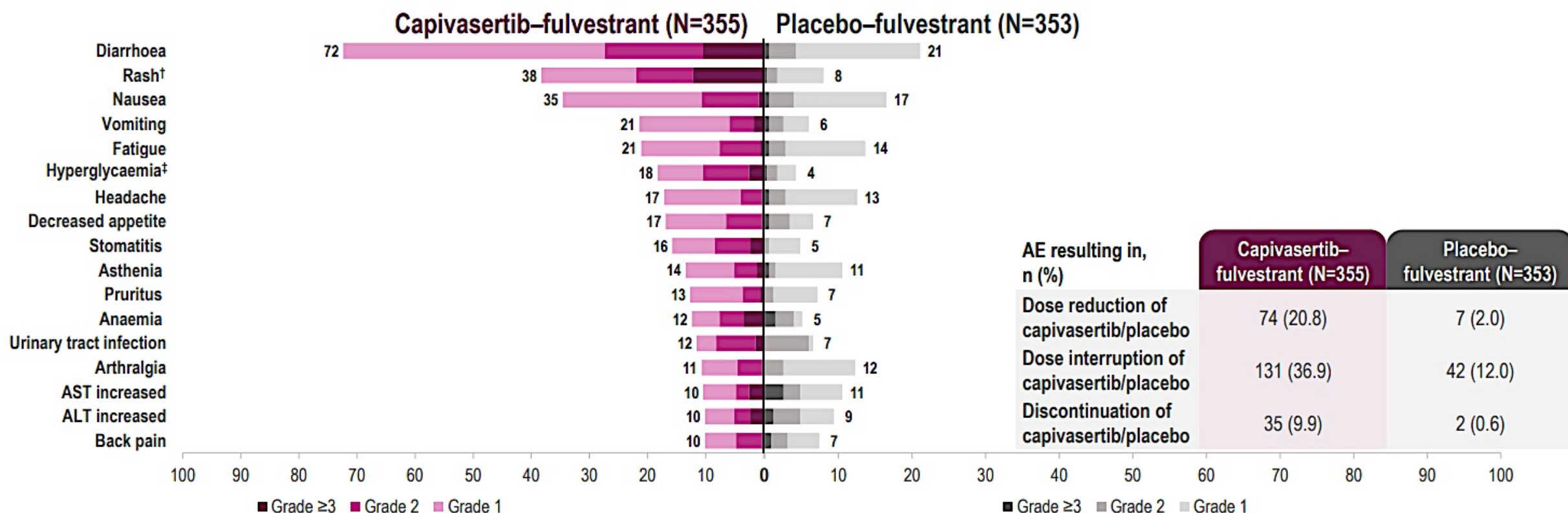
Number of patients at risk

Capivasertib-fulvestrant	355	344	329	320	308	297	279	267	254	238	218	203	194	184	178	165	156	141	130	122	110	104	100	85	67	53	38	27	11	5	1	0
Placebo-fulvestrant	353	335	317	306	288	297	263	248	232	221	204	190	186	174	165	162	153	143	132	128	122	113	109	90	69	53	40	24	12	6	2	0

Final DCO: 16 June 2025. Data maturity: 70.8%.

Safety* (overall population)

The safety profile of capivasertib–fulvestrant was consistent with the primary analysis; no new safety signals were identified since the primary data cut-off



At final analysis in the overall population, there were 12 (3.4%) patients in the capivasertib–fulvestrant arm and 11 (3.1%) in the placebo–fulvestrant arm still receiving study treatment

Number in bold indicates percentage total. *The listed events were reported as a single term in >10% of the patients for any grade in either group. AEs are reported regardless of the relationship to the study drugs. †Group term of rash includes the preferred terms of rash, rash macular, maculopapular rash, rash papular and rash pruritic. ‡Group term of hyperglycaemia includes the preferred terms of blood glucose increased and hyperglycaemia. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Summary of Trials with PI3Ki or AKTi

	SOLAR-1 ¹	Capitello-291 ^{2,3}	Inavo-120 ⁴
Agent	Alpelisib (α-selective PI3Ki)	Capivasertib (AKT1/2/3i)	Inavolisib (α-selective PI3Ki)
Treatment Arms	Fulv + Alpelisib/Pbo; P3 RCT	Fulv + Capivasertib/Pbo; P3 RCT	Fulv + Palbo + Inavo/Pbo; P3 RCT
KEY PARTICIPANT CHARACTERISTICS			
Patient Population	Recurrence/PD post AI PIK3CAm (60%)	≤ 2L ET for ABC; ≤ 1L chemo PIK3CAm/AKTm/mTORalt (41%)	1L Relapsed < 12 adj ET PIK3CAm only (100%)
1L/2L/3L	52%/47%/0%	10%/66%/21%	100% 1L
HgA1c	< 6.4%	< 8%	< 6.0%
Prior CDK4/6i	6%	69%	1%
OUTCOME			
mPFS (for PIK3CAm or AKT pway altered)	11 vs 5.7 mos (HR 0.65, 0.50-0.85)	7.3 vs 3.1 mos (HR 0.50, 0.38–0.65)	17.2 vs 7.3 mos (HR 0.42, 0.32-0.55)
OS (for PIK3CAm or AKT pway altered)	39.3 vs 31.4 mos (HR 0.86, 0.64-1.15)	28.5 vs 30.4 (HR 0.83, 0.63-1.10)	34 vs 27 mos (HR 0.67, 0.48-0.94)
TOXICITIES			
Toxicities	Diarrhea 58% (G3+ 7%) ↑Glucose 64% (G3+ 37%) Rash 36% (G3+ 10%)	Diarrhea 72% (G3+ 9%) ↑Glucose 16% (G3+ 2%) Rash 38% (G3+ 12%)	Diarrhea 48% (G3+ 4%) ↑Glucose 59% (G3+ 6%) Rash 25% (G3+ 0%)
D/C rate due to TRAEs	25%	13%	7%

1. Andre F *Ann Oncol* 2021; 32:208; 2. Turner et al *NEJM* 2023;388:2058; 3. Rugo et al. ESMO Breast 2026; 4. Jhaveri KL et al. *NEJM* 2025; 393:151.
Slide courtesy of Dr. Claudine Isaacs

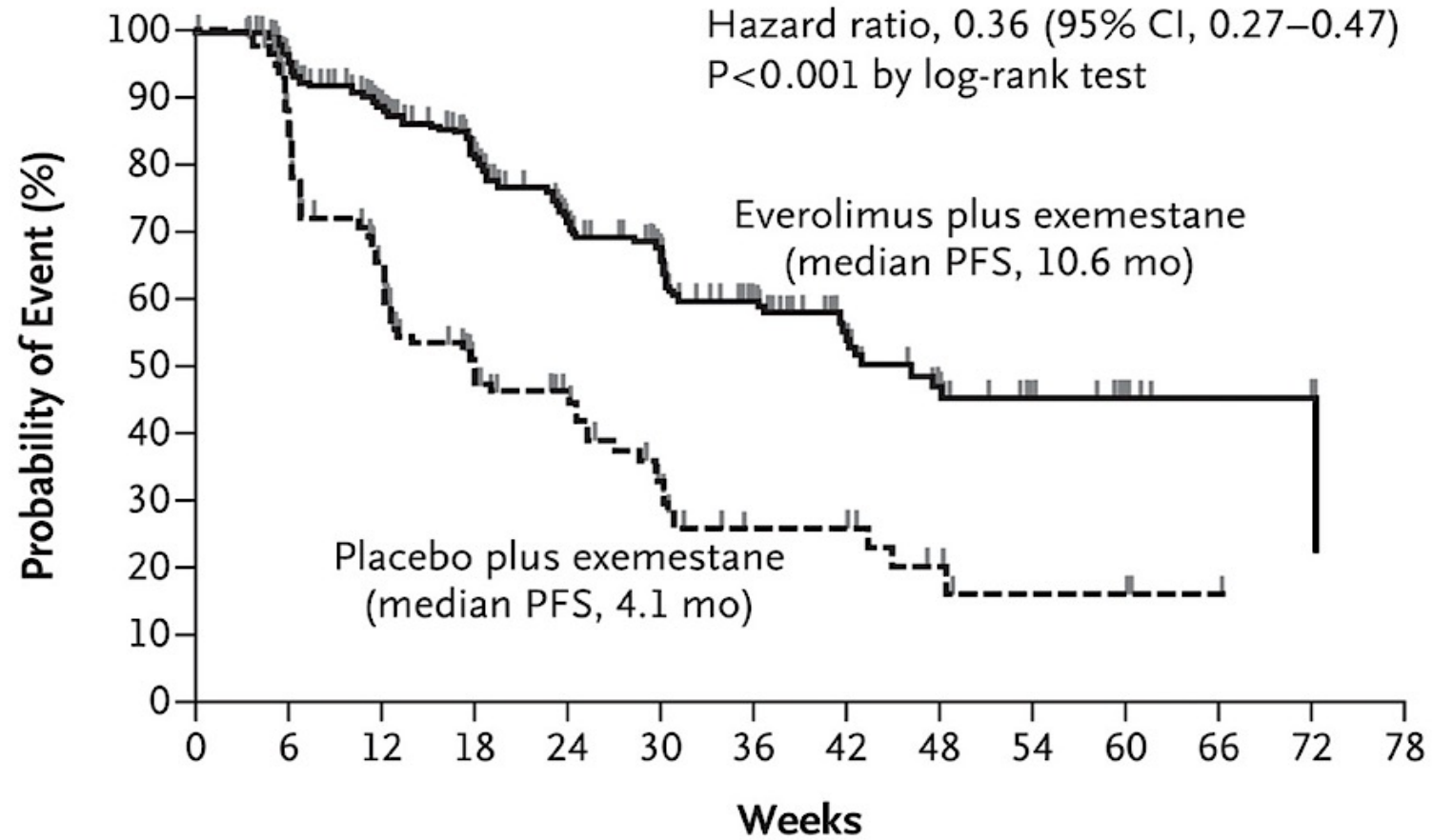
Phase III Trials of PI3K-pathway inhibition in PI3K altered or non-altered disease

Everolimus

BOLERO-2: Everolimus + Exemestane

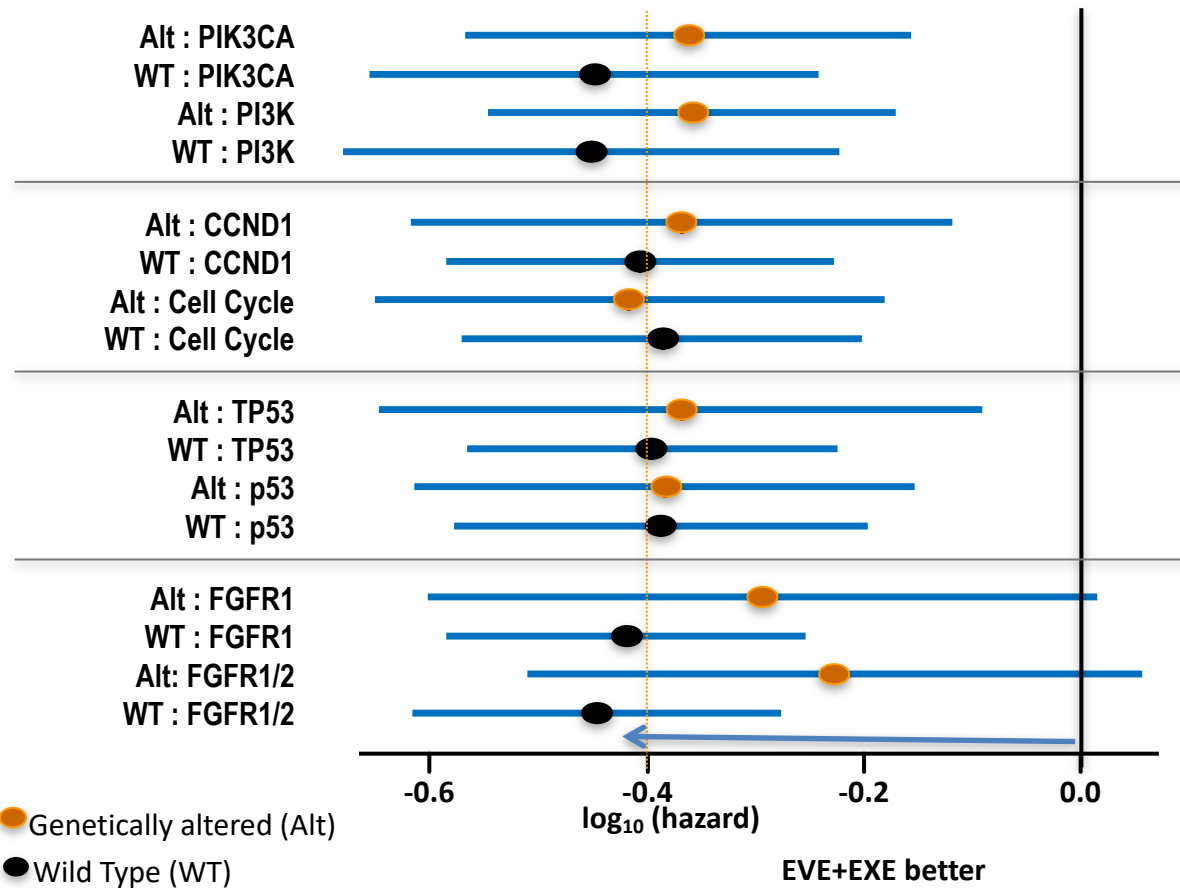
*******(no one had received prior CDK4/6i)*

B Central Assessment

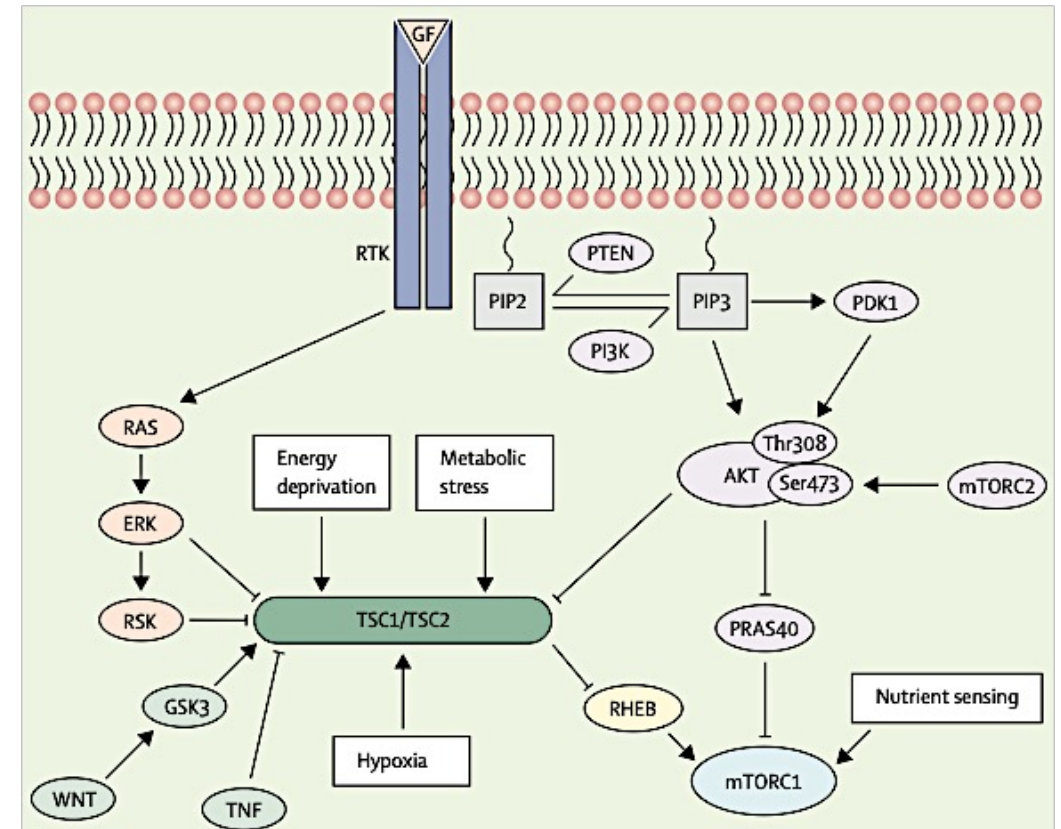


Everolimus benefit independent of *PIK3CA* mutation in BOLERO2

Efficacy not impacted by *PIK3CA* mutations



mTOR activity has many inputs not just PI3K/AKT signaling



**Triplet pathway inhibition in PIK3CA altered
or non-altered disease after CDK4/6i**

Gedatolisib 3 weeks on/1 week off + Palbo + ET

Dose Expansion (Previous CDK4/6i)

Group D	
Previous therapy	Second-line and higher; CDK inhibitor-pretreated
N	
Full analysis set	27
Response evaluable set	27
Study treatment (gedatolisib dosing schedule)	Gedatolisib, palbociclib, and fulvestrant (3 weeks on-1 week off)
Objective response, full analysis set	15 (55.6%; 38.2-72.0)
Objective response, response evaluable set	15 (55.6%; 38.2-72.0)
Objective response, response evaluable including unconfirmed partial response	17 (63.0% 45.3-78.3)
Median progression-free survival, * months (95% CI)	12.9 (7.4-16.7)
Progression-free survival at 12 months, % (95% CI)	53.2% (31.5-70.9)
Median duration of response, * months (95% CI)	12.6 (7.3-21.2)
PIK3CA status	
Wild type	15 (56%)
Mutant	11 (41%)
Objective response by PIK3CA status (response evaluable)	
Wild type	8 (53%)
Mutant	7 (64%)
Objective response by PIK3CA status (response evaluable)	
Wild type	9 (60%)
Mutant	8 (73%)

VIKTORIA-1 Study Design

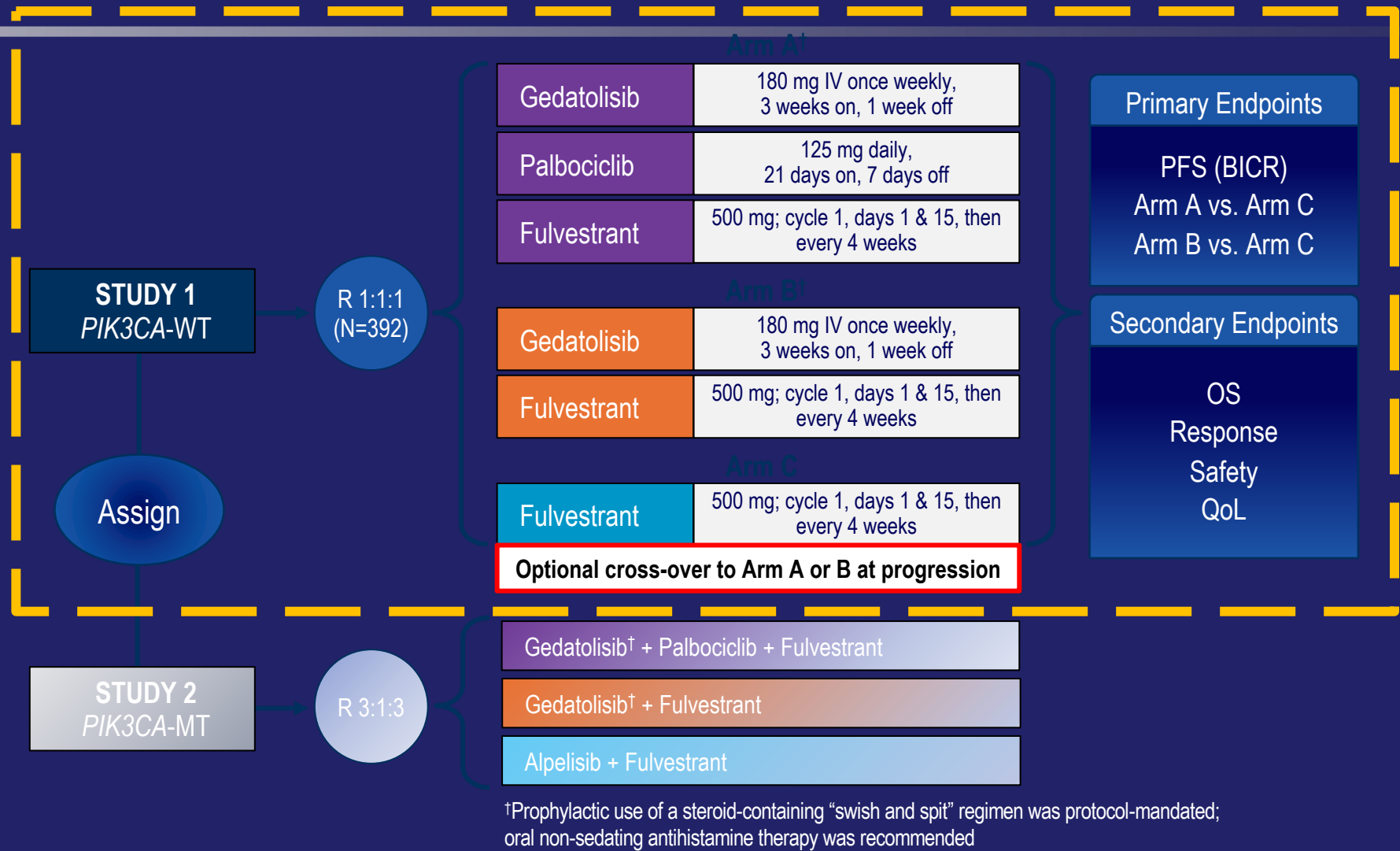
HR+/HER2-
Advanced Breast Cancer

Eligibility Criteria

- Pre- & postmenopausal women & men
- Progression on/after CDK4/6i + NSAI
≤2 lines of prior ET for ABC
- Measurable disease, RECIST v1.1
- Screening result for *PIK3CA* status
- No T2DM with HbA1c >6.4% or T1DM
- No prior mTORi, PI3Ki, or AKTi
- No prior chemotherapy for ABC

Stratification Factors

- Lung/liver metastases (yes/no)
- Time to progression on immediate prior therapy (≤ or >6 months)
- Region (US/Canada or ROW)

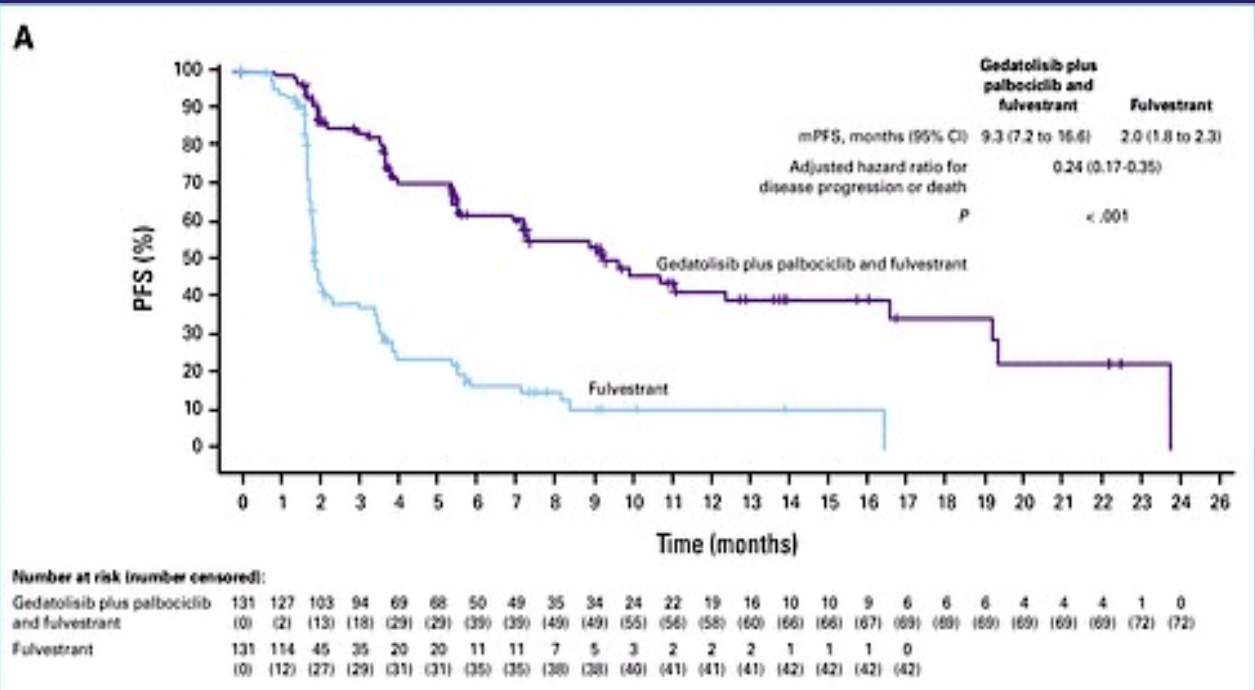


A Gennari

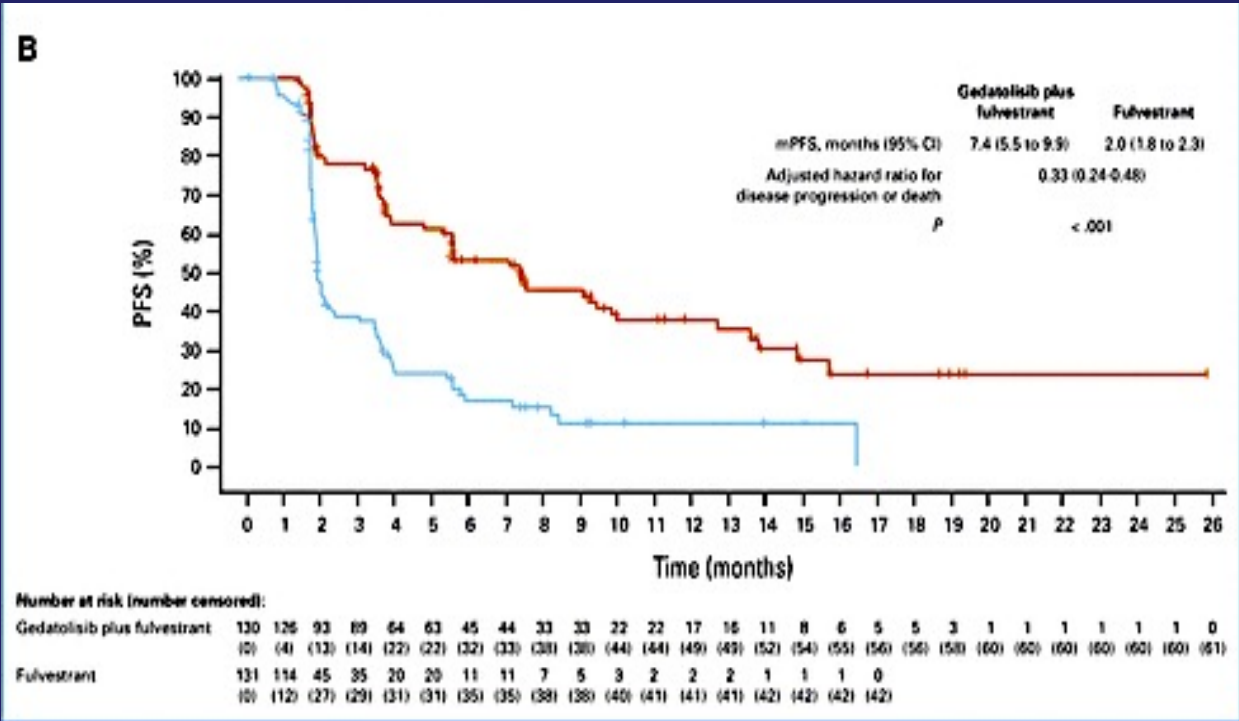
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VIKTORIA-1 Study 1 Results: PFS

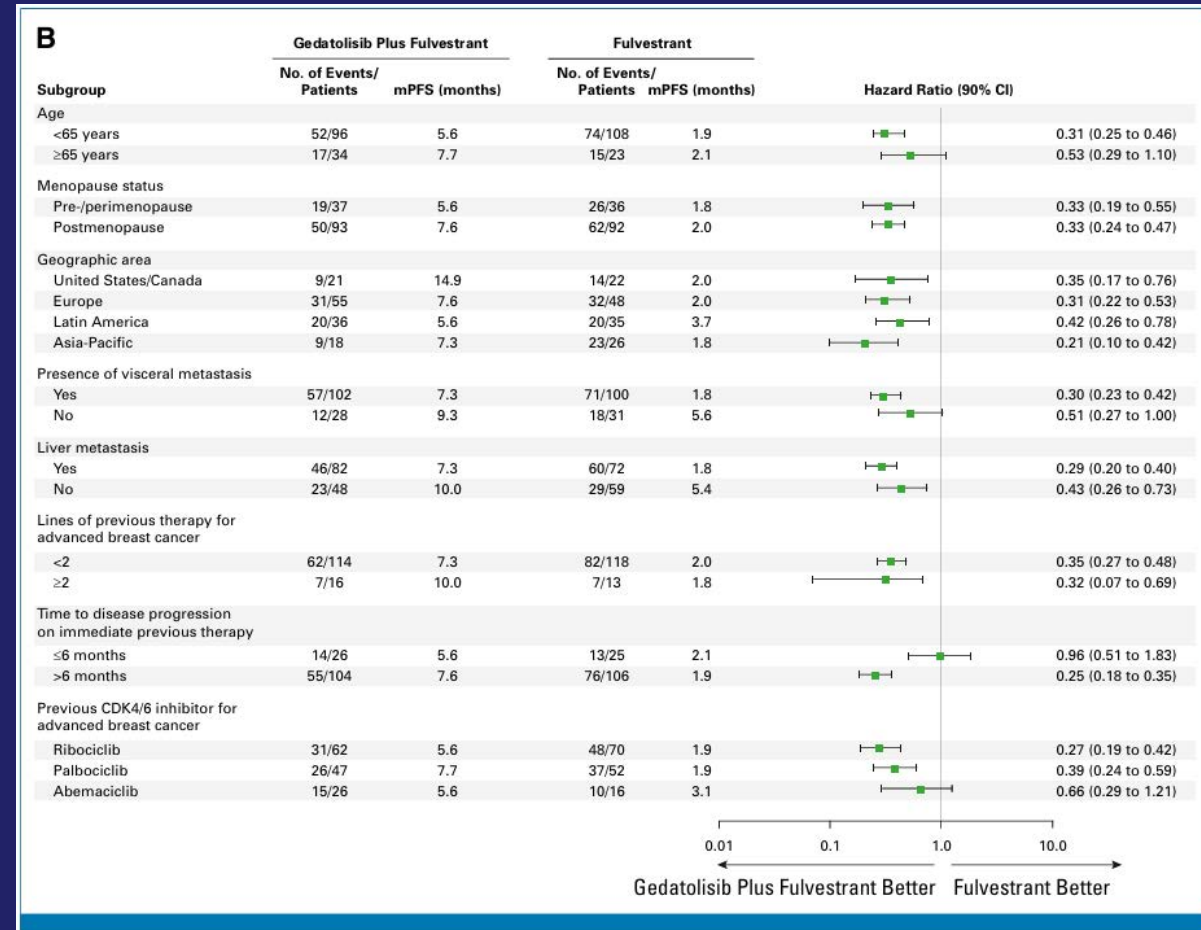
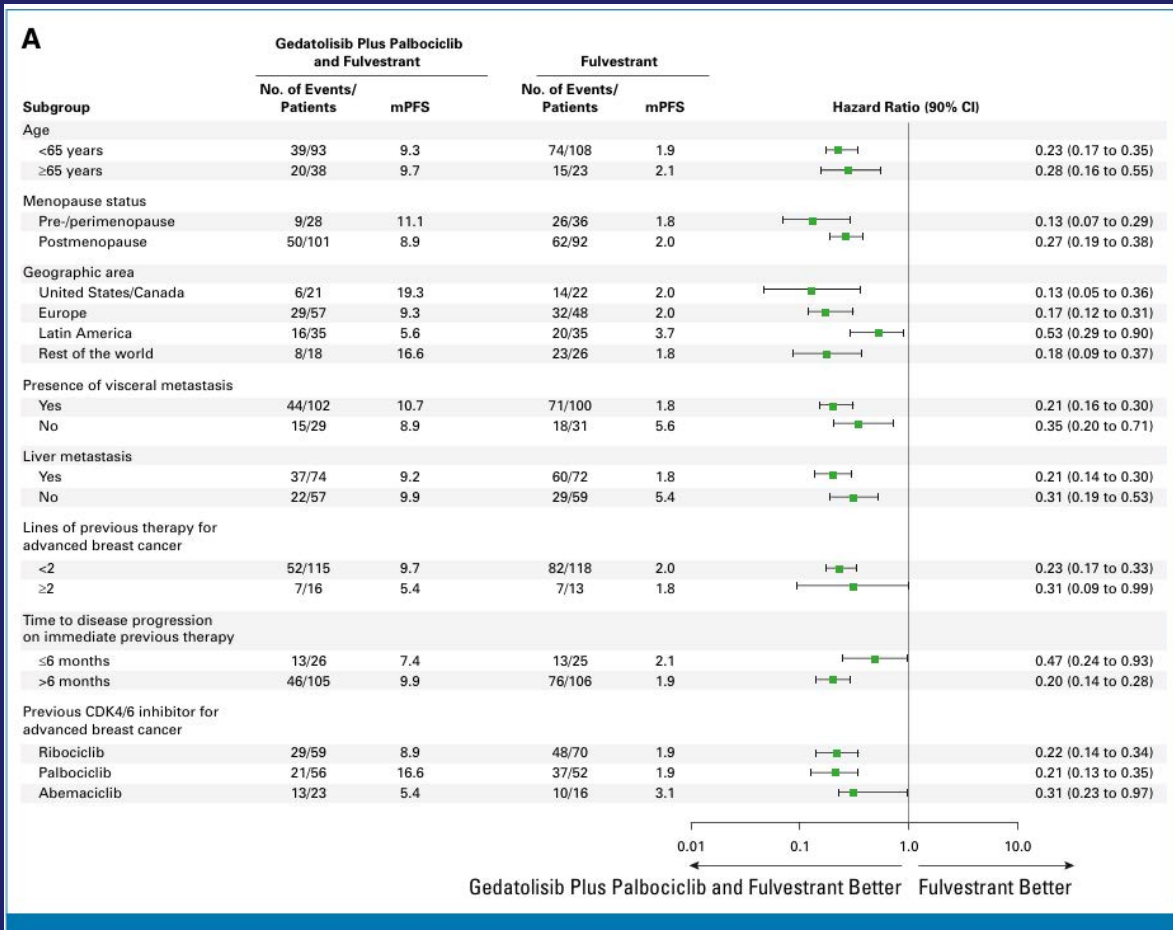
PFS Gedatolisib Triplet vs. Fulvestrant



PFS Gedatolisib Doublet vs. Fulvestrant

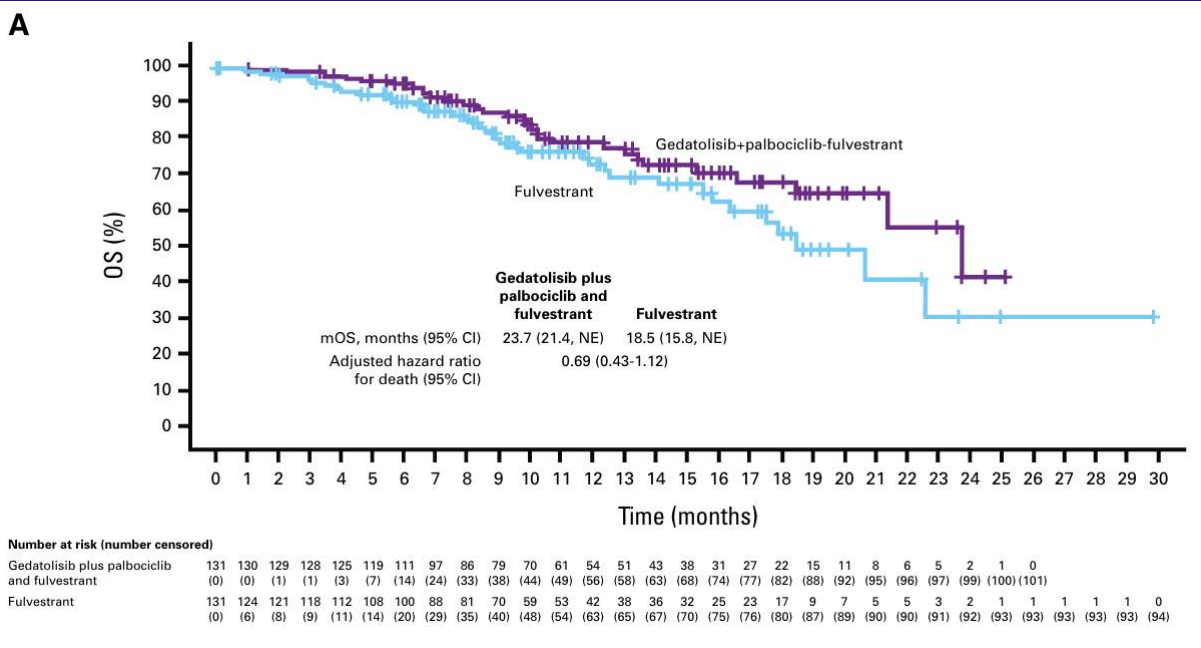


VIKTORIA-1 Study 1 Results: PFS Subgroup Analysis

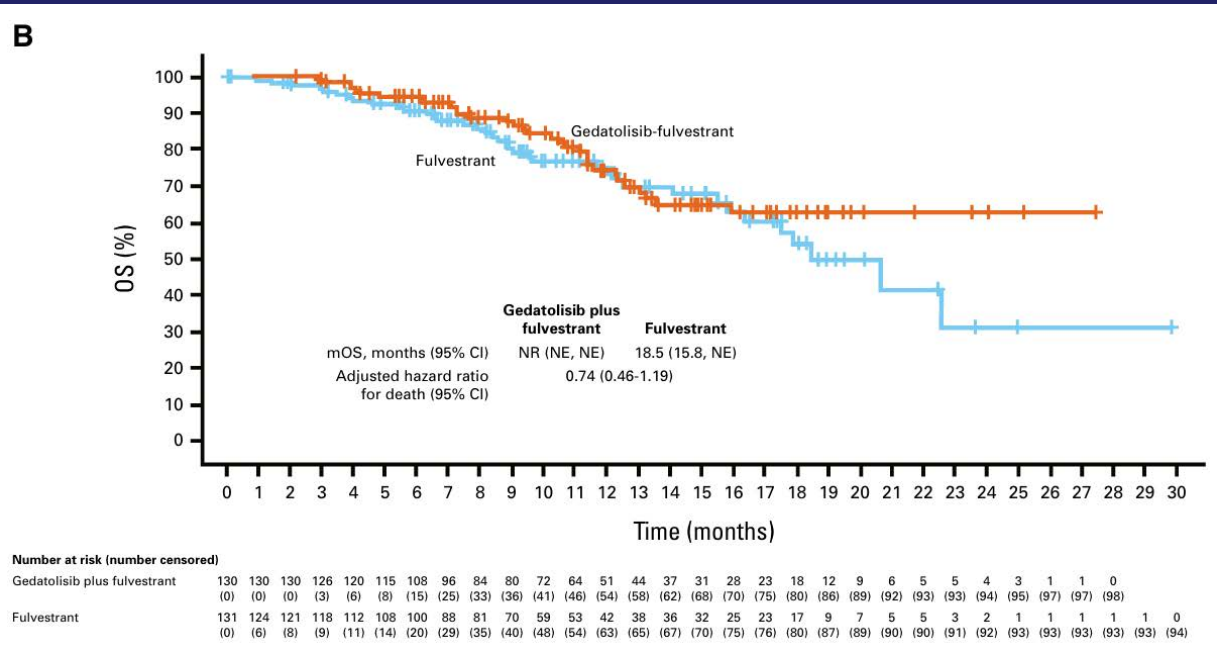


VIKTORIA-1 Study 1 Results: OS

PFS Gedatolisib Triplet vs. Fulvestrant



PFS Gedatolisib Doublet vs. Fulvestrant



VIKTORIA-1 Study 1 Results: TRAEs

TABLE 2. TRAEs (safety population)

Adverse Event, No. (%)	Gedatolisib Plus Palbociclib and Fulvestrant Group (n = 130)			Gedatolisib Plus Fulvestrant Group (n = 130)			Fulvestrant Group (n = 123)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Stomatitis ^a	90 (69.2)	25 (19.2)	0	74 (56.9)	16 (12.3)	0	0	0	0
Neutropenia ^b	85 (65.4)	68 (52.3)	13 (10.0)	2 (1.5)	0	1 (0.8)	1 (0.8)	1 (0.8)	0
Nausea	57 (43.8)	5 (3.8)	0	56 (43.1)	1 (0.8)	0	4 (3.3)	0	0
Rash ^c	36 (27.7)	6 (4.6)	0	42 (32.3)	7 (5.4)	0	0	0	0
Vomiting	36 (27.7)	2 (1.5)	0	30 (23.1)	0	0	1 (0.8)	0	0
Fatigue	29 (22.3)	2 (1.5)	0	27 (20.8)	1 (0.8)	0	5 (4.1)	0	0
Diarrhea ^d	22 (16.9)	2 (1.5)	0	16 (12.3)	1 (0.8)	0	0	0	0
Hyperglycemia ^d	12 (9.2)	3 (2.3)	0	15 (11.5)	3 (2.3)	0	0	0	0
Leukopenia ^d	14 (10.8)	8 (6.2)	1 (0.8)	0	0	0	0	0	0
Thrombocytopenia ^d	5 (3.8)	1 (0.8)	0	1 (0.8)	0	0	1 (0.8)	0	1 (0.8)
Pneumonitis ^d	4 (3.1)	0	0	5 (3.8)	1 (0.8)	1 (0.8)	0	0	0

NOTE. Shown are adverse events of any grade that occurred in at least 20% of the patients in any trial group unless otherwise noted. Data are for the safety analysis population, which included all the patients who had received at least one dose of any trial agent, with patients assessed in accordance with the trial agents they received. If a patient experienced more than one occurrence of an event, it was counted once for the highest grade.

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Phase III VIKTORIA-1 Trial Achieves Primary Endpoint in PIK3CA Mutant Cohort

Press Release: May 1, 2026

“Detailed data for the gedatolisib triplet and doublet regimens will be presented at a late-breaking abstract oral session at the 2026 ASCO Annual Meeting...

...positive topline results [were announced] from the *PIK3CA* mutant cohort of the Phase 3 VIKTORIA-1 clinical trial evaluating gedatolisib plus fulvestrant with or without palbociclib in patients with hormone receptor positive (“HR+”), human epidermal growth factor receptor 2 negative (“HER2-”), *PIK3CA* mutant locally advanced or metastatic breast cancer (“ABC”), following progression on or after treatment with a CDK4/6 inhibitor and an aromatase inhibitor.”

VIKTORIA-1 Study 2 Design

HR+/HER2- Advanced Breast Cancer

Eligibility Criteria

- Pre- & postmenopausal women & men
- Progression on/after CDK4/6i + NSAI
- ≤2 lines of prior ET for ABC
- Measurable disease, RECIST v1.1
- Screening result for *PIK3CA* status
- No T2DM with HbA1c >6.4% or T1DM
- No prior mTORi, PI3Ki, or AKTi
- No prior chemotherapy for ABC

Stratification Factors

- Lung/liver metastases (yes/no)
- TTP on immediate prior therapy (≤ or >6 months)
- Region (US/Canada or ROW)

STUDY 2
PIK3CA-MT

R 3:1:3
(N=362)

Assign

STUDY 1
PIK3CA-WT

R 1:1:1

Arm D†

Gedatolisib	180 mg IV once weekly, 3 weeks on, 1 week off
Palbociclib	125 mg daily, 21 days on, 7 days off
Fulvestrant	500 mg; cycle 1, days 1 & 15, then every 4 weeks

Arm E†

Gedatolisib	180 mg IV once weekly, 3 weeks on, 1 week off
Fulvestrant	500 mg; cycle 1, days 1 & 15, then every 4 weeks

Arm F

Alpelisib	300 mg orally daily for 4 weeks
Fulvestrant	500 mg; cycle 1, days 1 & 15, then every 4 weeks

Arm A: Gedatolisib[†] + Palbociclib + Fulvestrant

Arm B: Gedatolisib[†] + Fulvestrant

Arm C: Fulvestrant

Primary Endpoint

PFS (BICR)
Arm D vs. Arm F

Secondary Endpoints

OS
PFS (BICR,
Arm E vs. Arm F)
Response
Safety
QoL

[†]Prophylactic use of a steroid-containing “swish and spit” regimen was protocol-mandated; oral non-sedating antihistamine therapy was recommended

Abbreviations: ABC, advanced breast cancer; AKTi, protein kinase B inhibitor; BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; ET, endocrine therapy; HbA1c, hemoglobin A1c; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; IV, intravenous; MT, mutated; mTORi, mechanistic target of rapamycin inhibitor; NSAI, non-steroidal aromatase inhibitor; OS, overall survival; PFS, progression-free survival; PI3Ki, phosphatidylinositol 3-kinase inhibitor; QoL, quality of life; R, randomization; ROW, rest of world; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TTP, time to progression; WT, wild-type

VIKTORIA-1 Study 2 Design

HR+/HER2- Advanced Breast Cancer

Eligibility Criteria

- Pre- & postmenopausal
- Progression on/after
- ≤2 lines of prior ET for
- Measurable disease,
- Screening result for F
- No T2DM with HbA1c
- No prior mTORi, PI3K
- No prior chemotherapy

Stratification Factors

- Lung/liver metastases (yes/no)
- TTP on immediate prior therapy
- Region (US/Canada or ROW)

Arm D†

Gedatolisib

180 mg IV once weekly,
3 weeks on, 1 week off

Primary Endpoint

ICR)
Arm F

Endpoints

ICR,
Arm F)
nse
ty

steroid-containing
n was protocol-
dating
was recommended

receptor 2-
QoL, quality of life;

Tuesday, June 2, 2026

LBA1008 Hurvitz SA et al. A randomized, open-label, phase 3 study of gedatolisib + fulvestrant ± palbociclib vs standard of care in HR+/HER2-/PIK3CA-mutant (MT) advanced breast cancer (VIKTORIA-1 Study 2)

Safety

Toxicities comparison PI3Ki and AKTi

	<u>Inavolisib</u> + fulvestrant +palbociclib INAVO120		<u>Alpelisib</u> + fulvestrant SOLAR-1		<u>Capivasertib</u> + Fulvestrant CAPItello-291		<u>Ipatasertib</u> + fulvestrant FINER		<u>Gedatolisib</u> + fulvestrant ± palbociclib VIKTORIA-1	
	Any grade (%)	Grade ≥3 (%)	Any grade (%)	Grade ≥3 (%)	Any grade (%)	Grade ≥3 (%)	Any grade (%)	Grade ≥3 (%)	Any grade (%)	Grade ≥3 (%)
Hyperglycaemia	58.6	5.6	63.7	36.6	16.3	2.3	43.6	0	9.2	2.3
Diarrhea	48.1	3.7	57.7	6.7	72.4	9.3	87.1	16.1	16.9	1.5
Rash	25.3	0	35.6	9.9	38	12.1	25	1.6	27.7	4.6
Stomatitis	51.2	5.6	24.6	2.5	14.6	2	16.1	0	69.2	19.24
Nausea	27.8	0.6	44.7	2.5	34.6	0.8	58.9	0.8	43.8	3.8
AEs leading to study drug discontinuation	6.8		25		13		6.5		2.3	

Turner NC et al N Engl J Med. 2024; André F et al N Engl J Med. 2019;
 Turner NC et al N Engl J Med. 2023; Chia S et al ASCO 2025. responsibility of the author. Permission is required
 Hurvitz SA et al ESMO 2025.

Other novel therapies: Ipatasertib

CCTG MA.40/FINER Trial Design

Study population:

- Stage IV ER+/HER-2 negative breast cancer
- Prior line of systemic treatment with CDK 4/6i and AI
- ECOG PS 0–1
- Measurable or evaluable disease

*CDK 4/6i and AI progression →
randomization $\leq$ 4 weeks*

cfDNA for Stratification
(FoundationOne®Liquid CDx)

N=250

R
1:1

Ipatasertib + Fulvestrant

400 mg PO day 1-21

Stratification

- *PIK3CA/PTEN/AKT* altered vs wild type/unknown
- Primary versus secondary endocrine resistance

Placebo + Fulvestrant

Placebo PO day 1-21

Primary endpoint

- PFS by RECIST v1.1 in intent to treat (ITT) population

Key secondary endpoints

- PFS
 - by BICR in ITT
 - in AKT pathway altered cohort
 - OS
 - AEs
 - QoL
- Health Economics
 - Correlative

Today, we will present the
final PFS analysis from
ITT and biomarker
altered cohort

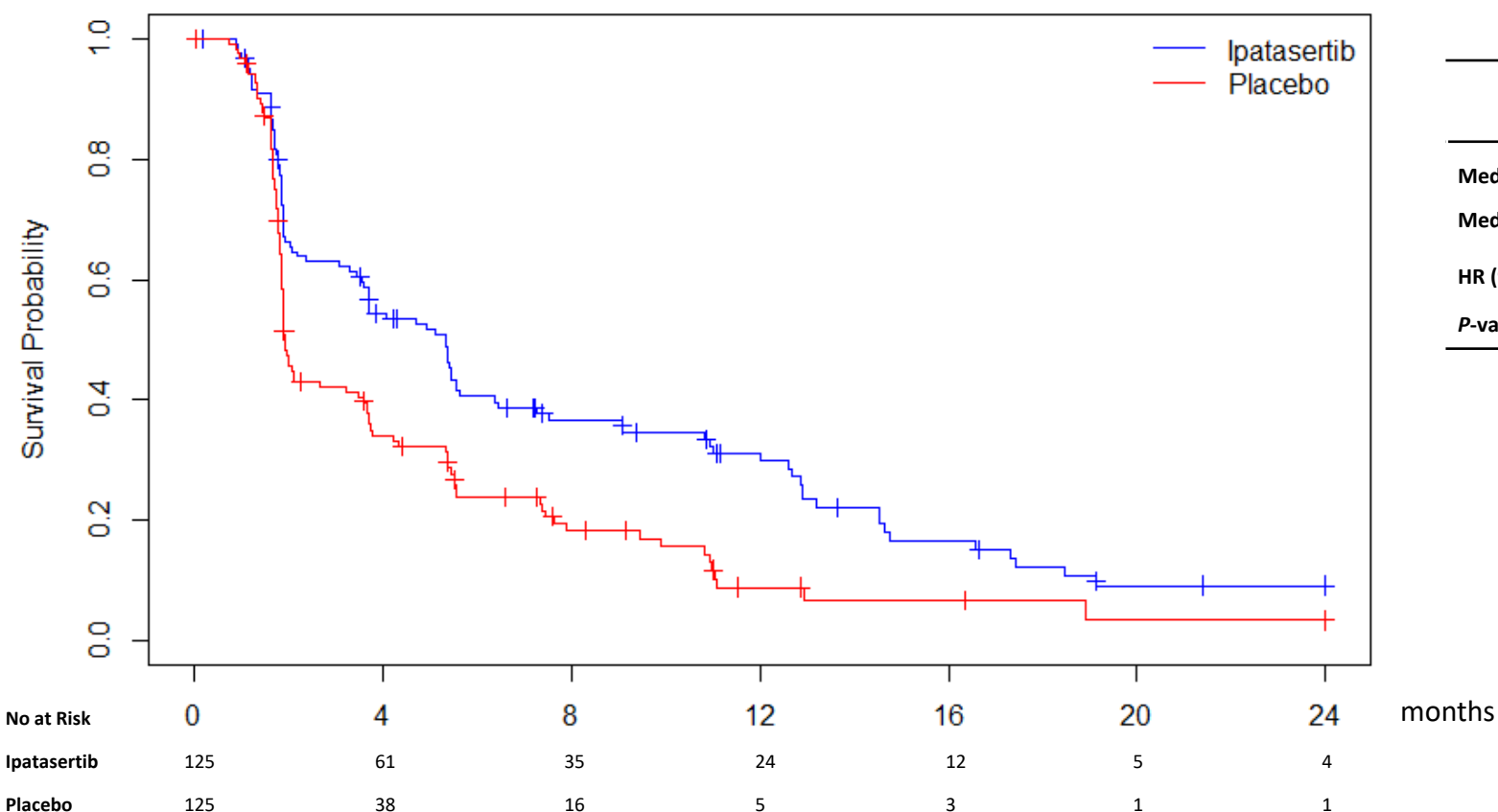
Fulvestrant 500 mg IM days 1 and 14 and 28
then q28 days

Baseline Characteristics

Characteristic	Ipatasertib + Fulvestrant (n=125)	Placebo + Fulvestrant (n=125)	Total Population (n=250)
Median age (range)	60 years (29-89 years)	59 years (33-83 years)	60 years (29-89 years)
Sex	Female 98.4%	Female 99.2%	Female 98.8%
Race			
White	78.4%	85.6%	82%
Asian	12.8%	9.6%	11.2%
Other	8.8%	4.8%	6.8%
ECOG Performance Status (0/1)	56%/44%	60.8%/39.2%	58.4%/41.6%
De novo MBC at presentation	39.2%	40%	39.6%
Sites of disease			
Bone only	16.8%	16.8%	16.8%
Lung and/or liver involvement	66.4%	66.4%	66.4%
Prior duration of CDK 4/6i			
< 6 months	8%	4%	6%
> 6 months	92%	96%	94%
PIK3CA/PTEN/AKT status			
Wild type/unknown	54.4%	56.8%	55.6%
Altered	45.6%	43.2%	44.4%

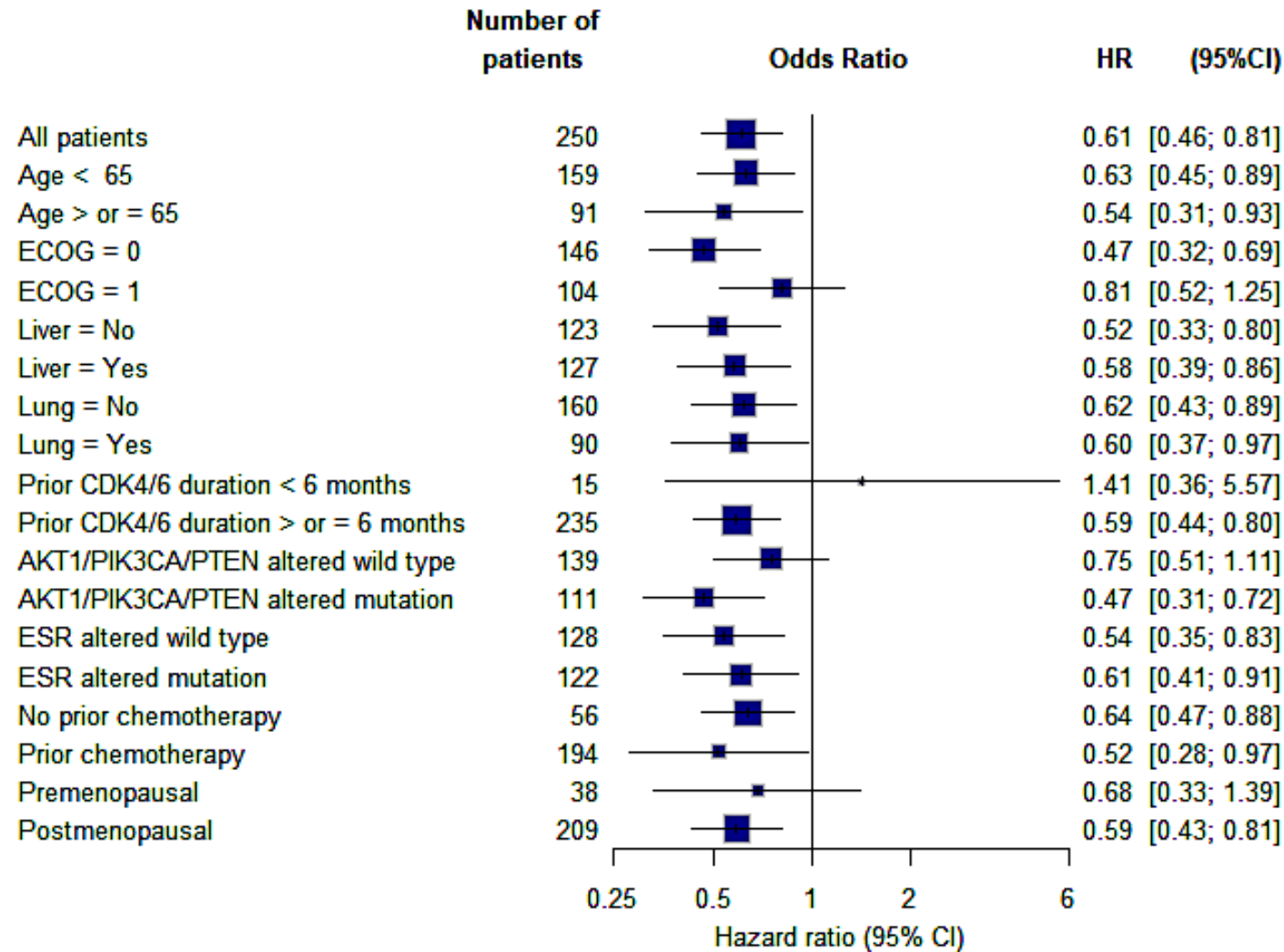
Unknown AKT pathway altered pathway: n=2 (<1%)

Results – Primary Endpoint – PFS in ITT (197 events)



	IPAT arm n=125	PBO arm n=125
Median follow-up: 15.2 months		
Median PFS (95% CI), months	5.32 (3.58-5.62)	1.94 (1.84-3.22)
HR (95% CI)	0.61 (0.46-0.81)	
P-value (2-sided)	0.0007	

Results – PFS ITT Forest Plot



Summary:

PI3K-Pathway Targeted Therapies in Endocrine Resistant Disease

PIK3CA mutated:

- Alpelisib plus fulvestrant approved
- Capivasertib plus fulvestrant approved (for any PI3K-pathway alteration)

PI3K-pathway agnostic (altered or non-altered)

- Everolimus plus endocrine therapy (exemestane, fulvestrant or tamoxifen)
- Coming soon: Everolimus + giredestrant?
- Coming soon: Gedatolisib + fulvestrant (+/- palbociclib)?
- Coming soon: Ipatasertib + fulvestrant?

Which treatment would you likely recommend next for a 65-year-old woman (PS 0) with ER/PR-positive, HER2-low (IHC 1+) mBC who develops multiple minimally symptomatic bone metastases after receiving ribociclib/letrozole?

Her biomarker testing results are:

- **PIK3CA-positive**
- **ESR1-negative**
- **BRCA wild type**

Age 65, PS 0; HER2 IHC 1+ BRCA wild-type mBC
Received ribociclib/letrozole for 2 years
PIK3CA-positive, ESR1-negative

		After receiving ribociclib/letrozole for 2 years	After receiving ribociclib/letrozole for 10 months
	Dr Hurvitz	Capivasertib + fulvestrant	Capivasertib + fulvestrant
	Dr Mayer	Capivasertib + fulvestrant	Capivasertib + fulvestrant
	Dr O'Shaughnessy	Capivasertib + fulvestrant	Abemaciclib + fulvestrant
	Dr Tolaney	Capivasertib + fulvestrant	Capivasertib + fulvestrant
	Dr Turner	Capivasertib + fulvestrant	Capivasertib + fulvestrant
	Dr Kaklamani	Capivasertib + fulvestrant	Capivasertib + fulvestrant

Which treatment would you recommend next for a 65-year-old woman (PS 0) with ER/PR-positive, HER2-low (IHC 1+) mBC who develops multiple minimally symptomatic bone metastases after receiving ribociclib/letrozole for 2 years?

Her biomarker testing results are:

- **PIK3CA-positive**
- **ESR1-positive**
- **BRCA wild type**

Age 65, PS 0; HER2-low (IHC 1+) BRCA wild-type mBC
Multiple minimally symptomatic bone metastases
PIK3CA-positive, ESR1-positive



Dr Hurvitz

Capivasertib + fulvestrant



Dr Mayer

Capivasertib + fulvestrant



Dr O'Shaughnessy

Elacestrant



Dr Tolaney

Elacestrant



Dr Turner

Capivasertib + fulvestrant



Dr Kaklamani

Elacestrant

Regulatory and reimbursement issues aside, which treatment would you likely recommend for a 65-year-old woman (PS 0) with ER/PR-positive, HER2-low (IHC 1+) mBC who develops multiple minimally symptomatic bone metastases after receiving ribociclib/letrozole for 2 years?

Her biomarker testing results are:

- **PIK3CA/AKT1/PTEN-negative**
- **ESR1-negative**
- **BRCA wild type**

Age 65, PS 0; HER2 IHC 1+, BRCA wild-type mBC

Received ribociclib/letrozole for 2 years; multiple minimally symptomatic bone metastases

PIK3CA/AKT1/PTEN-negative, ESR1-negative



Dr Hurvitz

Gedatolisib + fulvestrant + palbociclib



Dr Mayer

Abemaciclib + fulvestrant



Dr O'Shaughnessy

Everolimus + exemestane



Dr Tolaney

Abemaciclib + fulvestrant



Dr Turner

Everolimus + fulvestrant



Dr Kaklamani

Everolimus + fulvestrant

Regulatory and reimbursement issues aside, which treatment would you likely recommend next for a 65-year-old woman (PS 0) with ER/PR-positive, HER2-low (IHC 1+) BC who develops metastatic disease after 2 years of adjuvant anastrozole and receives ribociclib/fulvestrant for 2 years followed by disease progression.

Her biomarker testing results are:

- PIK3CA/AKT/PTEN-negative**
- ESR1-negative**
- BRCA wild type**

Age 65, PS 0; HER2 IHC 1+, metastatic PD 2 years after adjuvant anastrozole;
received ribociclib/fulvestrant for 2 years
PIK3CA/AKT1/PTEN-negative, ESR1-negative, BRCA wild type

		Multiple minimally symptomatic bone metastases	Multiple symptomatic visceral metastases and normal LFTs
	Dr Hurvitz	Gedatolisib + fulvestrant + palbociclib	Gedatolisib + fulvestrant + palbociclib
	Dr Mayer	Everolimus + exemestane	Gedatolisib + fulvestrant + palbociclib
	Dr O'Shaughnessy	Everolimus + exemestane	Gedatolisib + fulvestrant + palbociclib
	Dr Tolaney	Abemaciclib + fulvestrant	Gedatolisib + fulvestrant + palbociclib
	Dr Turner	Everolimus + fulvestrant	Trastuzumab deruxtecan
	Dr Kaklamani	Everolimus + exemestane	Everolimus + exemestane

How would you indirectly compare the global efficacy of gedatolisib to that of currently available agents targeting the PI3K/AKT/mTOR pathway for endocrine therapy-pretreated, HR-positive, HER2-negative mBC?



Dr Hurvitz

Gedatolisib is more efficacious



Dr Mayer

Gedatolisib is more efficacious



Dr O'Shaughnessy

Gedatolisib is more efficacious



Dr Tolaney

Gedatolisib is more efficacious



Dr Turner

About the same



Dr Kaklamani

Gedatolisib is more efficacious

Based on available and emerging data, would you like to have access to gedatolisib for your patients with endocrine therapy-pretreated, HR-positive, HER2-negative mBC at the current time?

		PIK3CA mutant	PIK3CA wild type
	Dr Hurvitz	Yes	Yes
	Dr Mayer	Yes	Yes
	Dr O'Shaughnessy	Yes	Yes
	Dr Tolaney	Yes	Yes
	Dr Turner	No	Yes
	Dr Kaklamani	Yes	Yes

If gedatolisib were available today, where in the therapeutic sequence and for which types of patients would you most likely employ it for ...?

	PIK3CA-mutant disease	PIK3CA wild-type disease
 Dr Hurvitz	After a CDK4/6 inhibitor	After a CDK4/6 inhibitor
 Dr Mayer	Post-CDK and weekly IV therapy acceptable to patient	Post-CDK and not using everolimus based regimen
 Dr O'Shaughnessy	After a CDK4/6i and after capivasertib or inavolisib or other oral PI3K pathway inhibitors	Without liver mets: after a CDK4/6i and everolimus. With liver mets: instead of everolimus (+ palbo and fulvestrant)
 Dr Tolaney	After-progression on CDK4/6 inhibitor	Maybe if ESR1 wt and lots of visceral mets
 Dr Turner	Not used	ESR1 wt
 Dr Kaklamani	Some second line	Need to see data

CDK4/6i = CDK4/6 inhibitor

If gedatolisib were available today, for which types of patients would you most likely combine it with fulvestrant alone versus fulvestrant/palbociclib?



Dr Hurvitz

**PIK3CA WT: triplet for most; PIK3CA mut:
doublet reasonable for most but awaiting long-term data**



Dr Mayer

Would likely select the triplet



Dr O'Shaughnessy

Likely would mainly use the triplet



Dr Tolaney

**Would use triplet with palbociclib unless Rb mutation,
as it doesn't add much toxicity**



Dr Turner

Would combine with fulvestrant alone



Dr Kaklamani

Triplet for most; doublet for older patients

Agenda

Module 1: Current and Future Roles of Agents Targeting the PI3K/AKT/mTOR Pathway and Oral SERDs in First-Line Therapy for HR-Positive, HER2-Negative Metastatic Breast Cancer (mBC) — Dr Turner

Module 2: Role of Oral SERD Monotherapy in the Treatment of Progressive HR-Positive, HER2-Negative mBC — Dr O'Shaughnessy

Module 3: Potential Use of Oral SERD-Containing Combination Regimens in Managing Progressive HR-Positive, HER2-Negative mBC — Dr Mayer

Module 4: Clinical Utility of Agents Targeting the PI3K/AKT/mTOR Pathway for Patients with Progressive HR-Positive, HER2-Negative mBC — Dr Hurvitz

Module 5: Potential Use of Oral SERDs for HR-Positive, HER2-Negative Localized BC — Dr Tolaney



MAY 2026

Adjuvant SERD Therapy: The Road Ahead

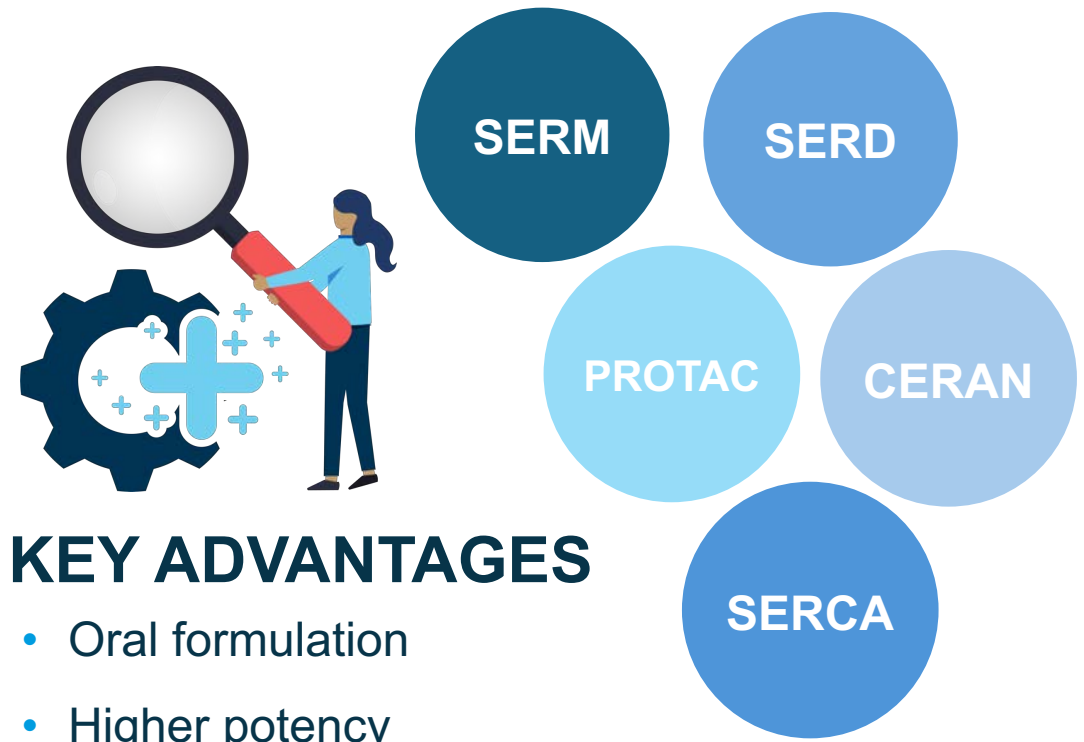
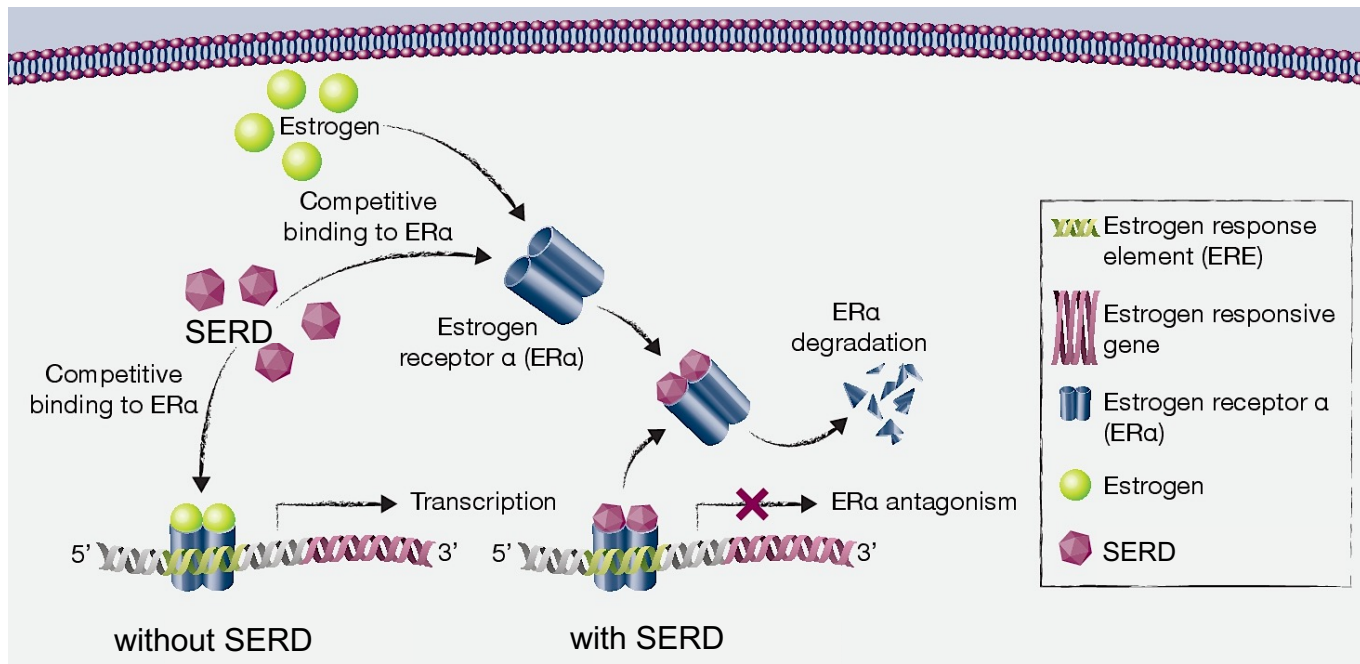
Sara M. Tolaney, MD, MPH

Division of Breast Oncology, Dana-Farber Cancer Institute



Novel Endocrine Therapies May Address Endocrine Resistance in MBC

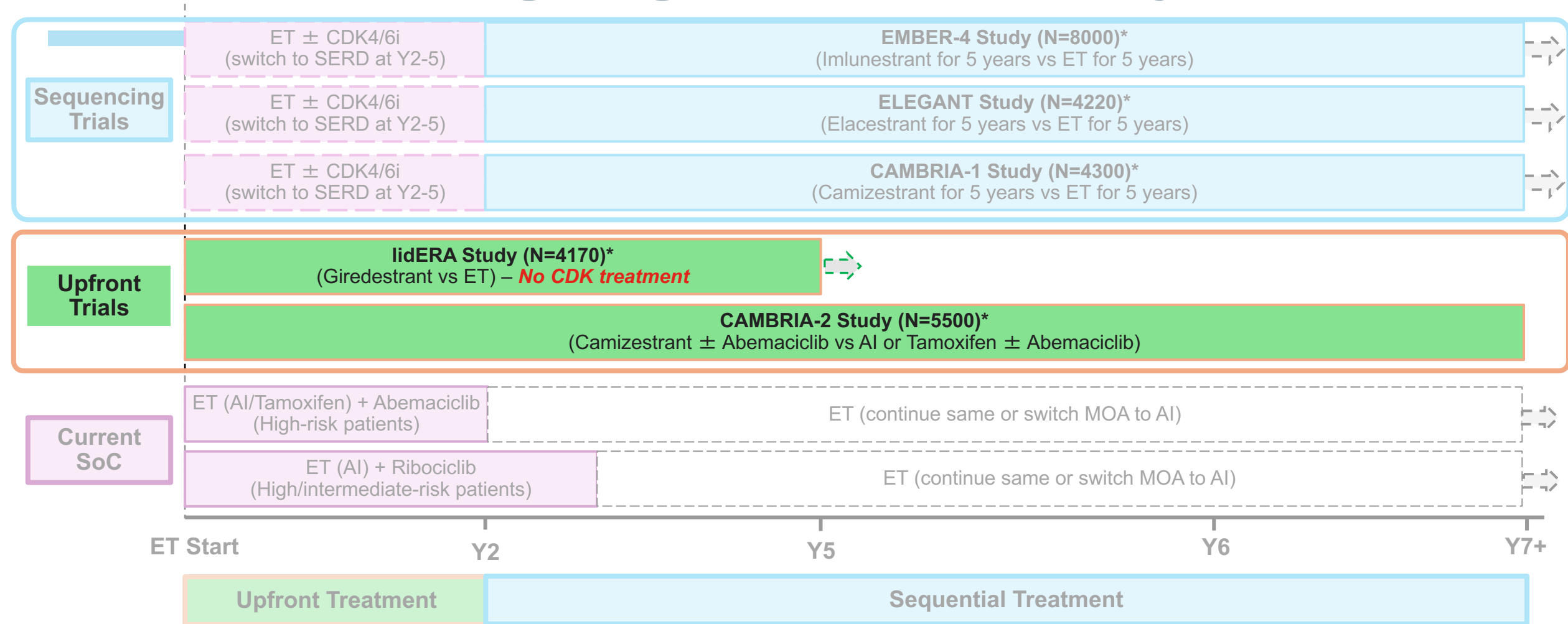
SERD Mechanism of Action



KEY ADVANTAGES

- Oral formulation
- Higher potency
- Activity in ESR1 mutant MBC
- Activity in post-ET and CDK4/6i treated patients
- Can be well tolerated

Overview of Ongoing Research in Adjuvant ET^{a,1-14}



^a"Intermediate/high-risk patients" definitions varied across studies. *Indication currently not approved or included in treatment recommendations.

AI, aromatase inhibitor; CDK, cyclin-dependent kinase; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; EBC, early breast cancer; ET, endocrine therapy; HR, hormone receptor; SoC, standard of care; Y, year.

- <https://clinicaltrials.gov/study/NCT05514054>. (Accessed February 10, 2026).
- <https://www.lillyoncologypipeline.com/molecule/selective-er-degrader/clinical-trial/NCT05514054>. (Accessed February 10, 2026).
- Jhaveri K, et al. Oral presentation at: SABCS 2025. Abstract GS3-08.
- <https://clinicaltrials.gov/study/NCT06492616>. (Accessed February 10, 2026).
- Bardia A, et al. Poster presentation at: ASCO 2025. Abstract TPS619.
- <https://clinicaltrials.gov/study/NCT05774951> (Accessed February 10, 2026).
- <https://clinicaltrials.gov/study/NCT04961996>. (Accessed February 10, 2026).
- Bardia AL, et al. Oral presentation at: SABCS 2025. Abstract GS1-10.
- <https://clinicaltrials.gov/study/NCT05952557>. (Accessed February 10, 2026).
- Hamilton EP, et al. Future Oncol. 2025;21(7):795-806.
- Loibl S, et al. Ann Oncol. 2024;35(2):159-182.
- Freedman RA, et al. J Clin Oncol. 2024;42(18):2233-2235.
- NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. Version 2.2026.
- Park-Simon T-W, et al. Breast Care (Basel). 2025;20(3):189-207.

lidERA Breast Cancer Study Design

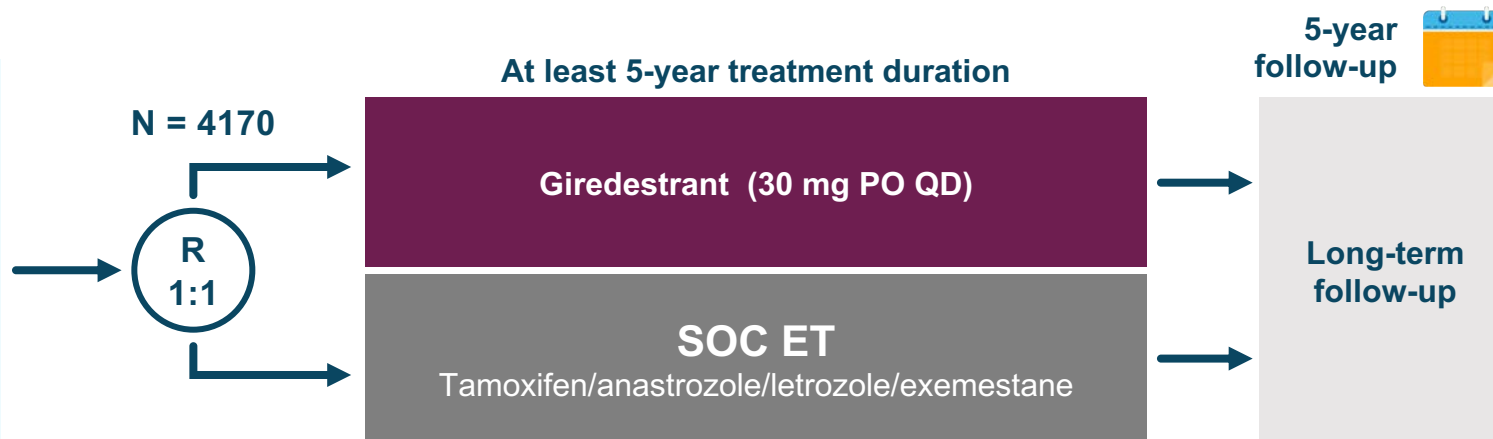
A global, randomized, open-label, multicenter Phase III trial

Key Eligibility Criteria

- Participants with ER+, HER2-negative early breast cancer
- Stage I–III disease (anatomical)
 - pN0 and pT > 1 cm with Grade 3, or Ki67 ≥ 20%, or high score on genomic assay,* or pT4N0
 - Node-positive
- Pre- or post-menopausal†
- Breast cancer surgery within 12 months
- (Neo)adjuvant chemotherapy if indicated for mBC‡

Stratification Factors

- Risk: Medium-‡ vs high-risk§ Stage I–III breast cancer
- Region: USA/Canada/Western Europe vs Asia–Pacific vs RoW
- Previous chemotherapy: No vs yes
- Menopausal status: Pre-menopausal vs post-menopausal



Primary Endpoint

- IDFS (excluding second primary non-breast cancer)

Key secondary endpoints

- DFS, DRFI, IDFS (including second primary non-breast invasive cancer with exception of non-melanoma skin cancers and *in situ* carcinomas of any site), LRRFI, OS, safety

Giredestrant is currently also being investigated in combination with abemaciclib in the adjuvant setting (lidERA Breast Cancer substudy 1)

Enrollment: August 2021 to September 2023. Up to 12 weeks of ET ± CDK4/6i were allowed. ER+ was defined as ≥ 1% positive cells by immunohistochemistry. * OncotypeDx ≥ 26 or high-risk MammaPrint.

† Pre-menopausal patients on aromatase inhibitors or giredestrant had to receive ovarian function suppression with an approved luteinizing hormone-releasing hormone agonist. ‡ Medium risk: pN0 and primary tumor > 1 cm with high-risk biologic features (Grade 3, or Ki67 ≥ 20%, or high score on genomic assay [if available]) and pN1 with low-risk biologic features (Grade 1/2 and Ki67 < 20% and tumor ≤ 5 cm and low score on genomic assay [if available]). § High risk: pT4, or pN2, or pN3 and pN1 with high-risk biologic features (Grade 3, or Ki67 ≥ 20%, or tumor > 5 cm, or high score on genomic assay [if available]).

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DFS, disease-free survival; DRFI, distant recurrence-free interval; ER+, estrogen receptor-positive; ET, endocrine therapy; IDFS, invasive disease-free survival; LRRFI, locoregional recurrence-free interval; OS, overall survival; PO, orally; QD, once daily; R, randomization; RoW, rest of the world; SOC, standard-of-care.

ClinicalTrials.gov number, NCT04961996. Adapted from Geyer CE, *et al.* ASCO 2023 (TPS616), with permission.

Presented by: Aditya L. Bardia, MD.

IdERA Breast Cancer Study Design

A global, randomized, open-label, multicenter Phase III trial

Medium Risk:

- pN0 and T >1 cm with high-risk features (G3, or Ki67 $\geq$ 20%, or high genomic score)
- pN1 with low-risk features (G1/2 and Ki67 < 20% and tumor $\leq$ 5 cm and low genomic score)

High Risk:

- pT4
- pN2-3
- pN1 with high-risk features (G3, or Ki67 $\geq$ 20%, or tumor > 5 cm, or high genomic score)

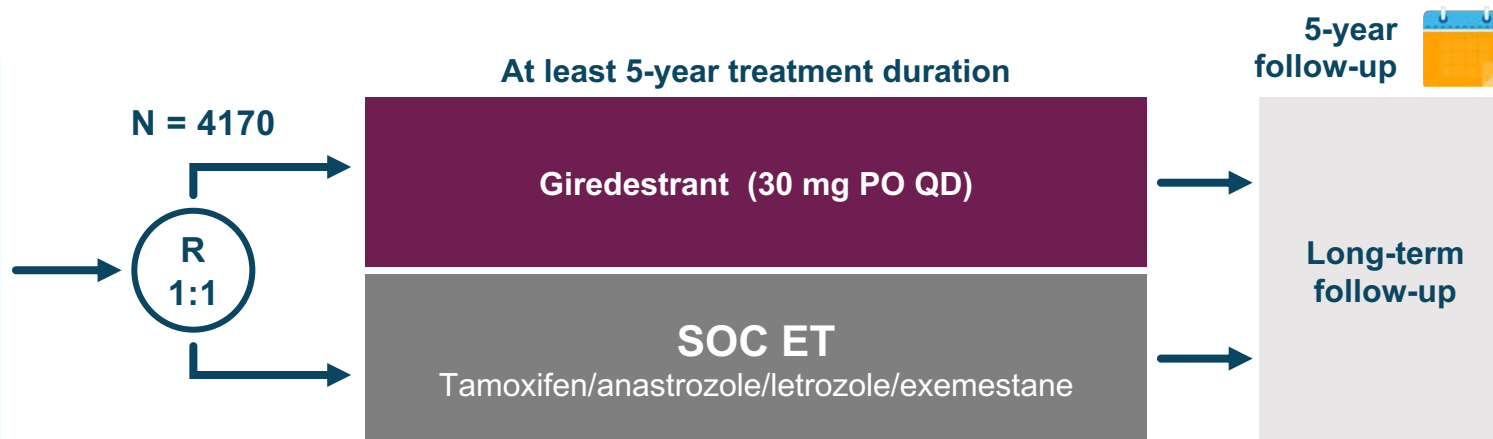


IdERA Breast Cancer Study Design

A global, randomized, open-label, multicenter Phase III trial

Key Eligibility Criteria

- Participants with ER+, HER2-negative early breast cancer
- Stage I–III disease (anatomical)
 - pN0 and pT > 1 cm with Grade 3, or Ki67 ≥ 20%, or high score on genomic assay,* or pT4N0
 - Node-positive
- Pre- or post-menopausal†
- Breast cancer surgery within 12 months



Medium Risk:

- pN0 and T > 1 cm with high-risk features (G3, or Ki67 ≥ 20%, or high genomic score)
- pN1 with low-risk features (G1/2 and Ki67 < 20% and tumor ≤ 5 cm and low genomic score)

High Risk:

- pT4
- pN2-3
- pN1 with high-risk features (G3, or Ki67 ≥ 20%, or tumor > 5 cm, or high genomic score)



Baseline Demographics and Characteristics

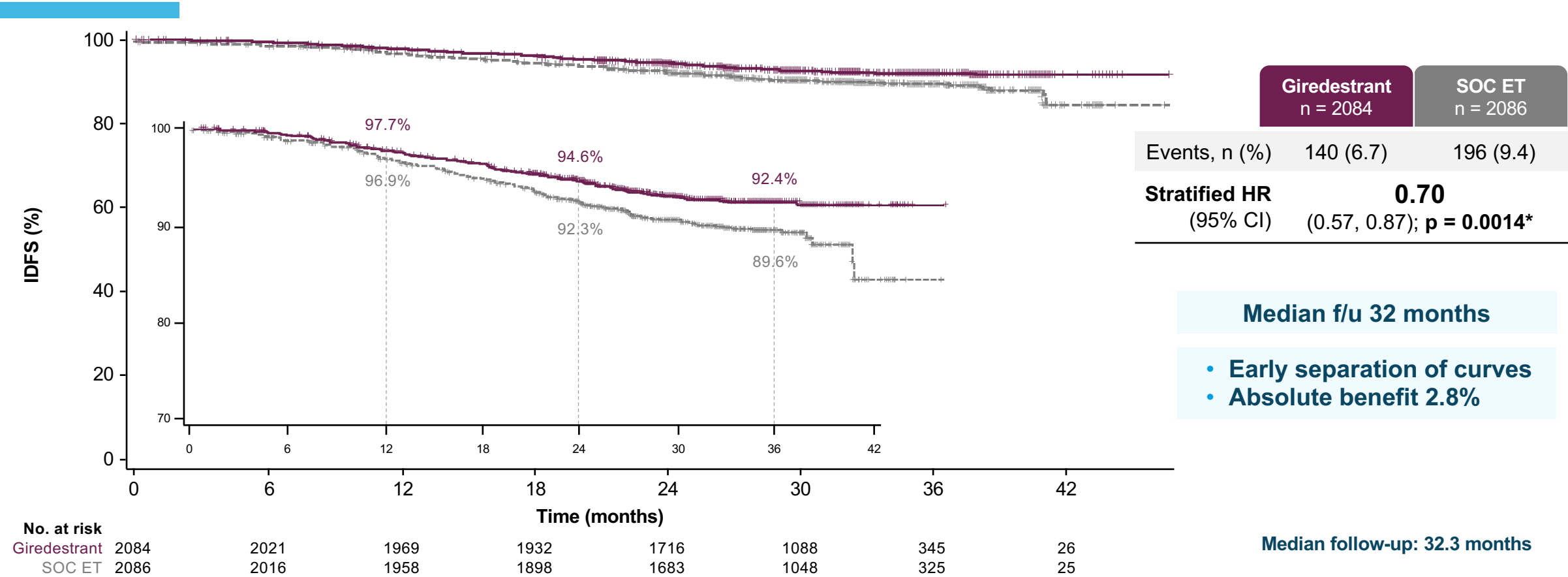
	Giredestrant n = 2084	SOC ET n = 2086
Median age, years (range)	54.0 (22–91)	54.0 (25–89)
Female sex, n (%)	2073 (99.5)	2075 (99.5)
Race, n (%)		
American Indian or Alaska Native	77 (3.7)	62 (3.0)
Asian	461 (22.1)	467 (22.4)
Black or African American	50 (2.4)	50 (2.4)
Other*	263 (12.6)	232 (11.1)
White	1233 (59.2)	1275 (61.1)
Region, n (%)		
Asia–Pacific	544 (26.1)	544 (26.1)
USA/Canada/Western Europe	860 (41.3)	905 (43.4)
Latin America/Africa/Eastern Europe	680 (32.6)	637 (30.5)
Menopausal status, n (%)[†]		16% tamoxifen
Pre-menopausal	849 (41.0)	838 (40.4)
Post-menopausal	1220 (59.0)	1236 (59.6)

	Giredestrant n = 2084	SOC ET n = 2086
ER status, n (%)[‡]		
Low-positive (1–10% of cells positive)	45 (2.2)	52 (2.5)
Positive (> 10% of cells positive)	2030 (97.8)	2031 (97.5)
AJCC stage at surgery, n (%)[§]		
I	254 (12.3)	283 (13.6)
II	1013 (49.0)	950 (45.7)
III	799 (38.7)	844 (40.6)
Nodal status, n (%) on surgical specimen		
pN0	449 (21.6)	441 (21.2)
pN1	968 (46.6)	953 (45.7)
pN2–3	662 (31.8)	691 (33.1)
Risk, n (%)		
High	1448 (69.5)	1447 (69.4)
Medium	636 (30.5)	639 (30.6)
Previous chemotherapy, n (%)		
No	396 (19.0)	450 (21.6)
Yes	1688 (81.0)	1636 (78.4)

Baseline demographics and characteristics were balanced.

Data cutoff: August 8, 2025. * “Other” refers to “multiple”, “Native Hawaiian or Other Pacific Islander”, “not reported”, or “unknown”. † Twenty-seven patients had unknown menopausal status (15 in the giredestrant arm and 12 in the SOC ET arm). ‡ Twelve patients had unknown ER status (nine in the giredestrant arm and three in the SOC ET arm). § One patient had Stage 0 disease (SOC ET arm); 26 had unknown Stage (18 in the giredestrant arm and eight in the SOC ET arm). || Six patients had unknown nodal status (five in the giredestrant arm and one in the SOC ET arm). AJCC, American Joint Committee on Cancer; ER, estrogen receptor; ET, endocrine therapy; SOC, standard-of-care.

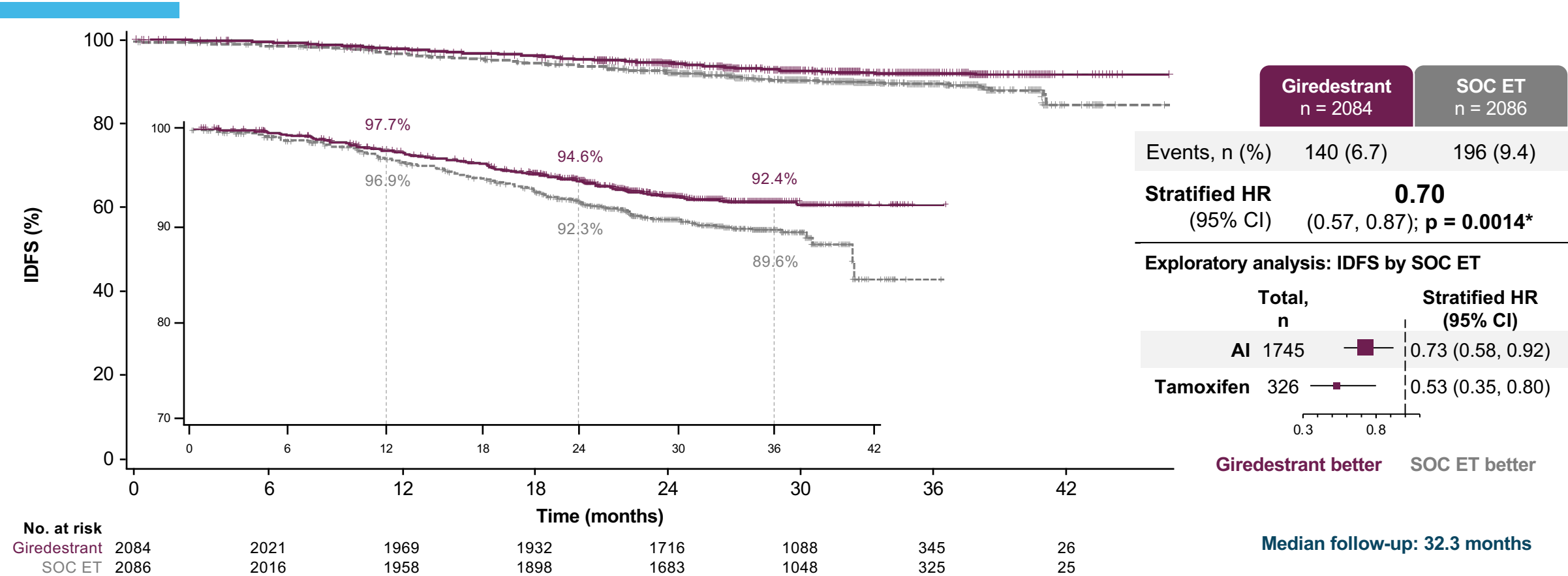
lidERA Primary Endpoint: IDFS



Statistically significant and clinically meaningful improvement in IDFS:
Giredestrant reduced the risk of invasive disease recurrence or death by 30% compared with SOC ET.

Data cutoff: August 8, 2025. Median follow-up, 32.4 months in the giredestrant arm and 32.3 months in the SOC ET arm; maximum follow-up, 46.6 months and 46.3 months, respectively. * Log-rank (2-sided). p-value boundary for IDFS interim analysis was 0.0217 (2-sided). AI, aromatase inhibitor; CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; IDFS, invasive disease-free survival; SOC, standard-of-care.

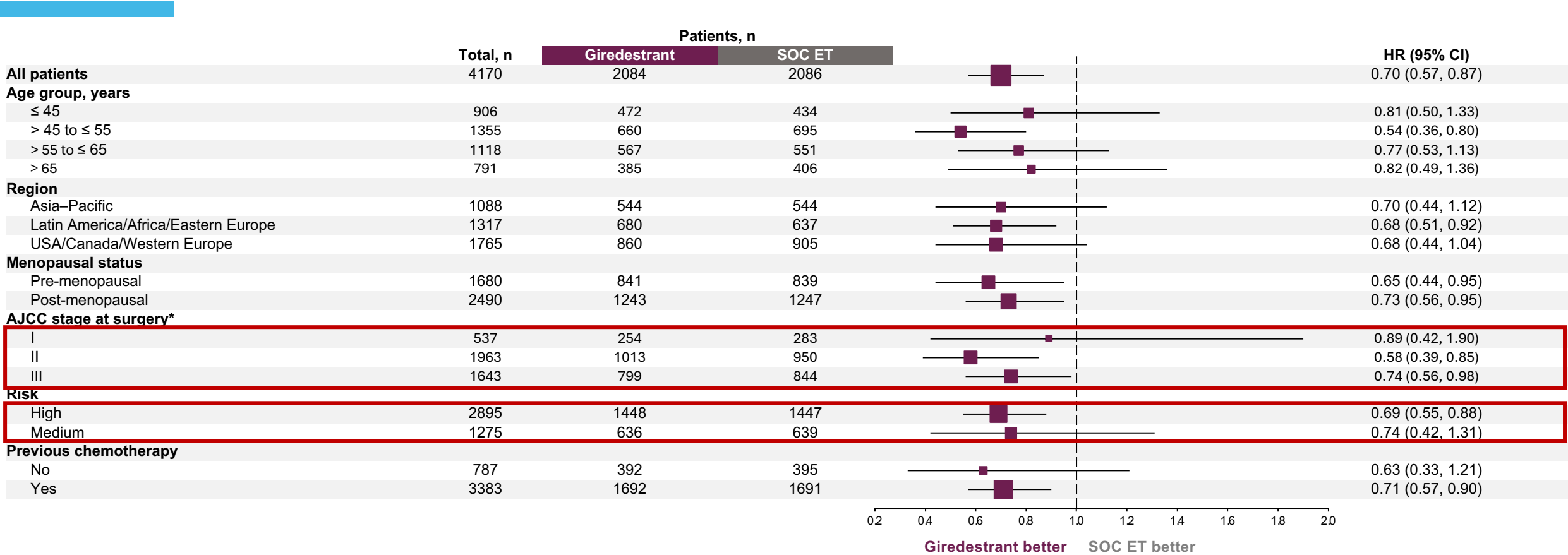
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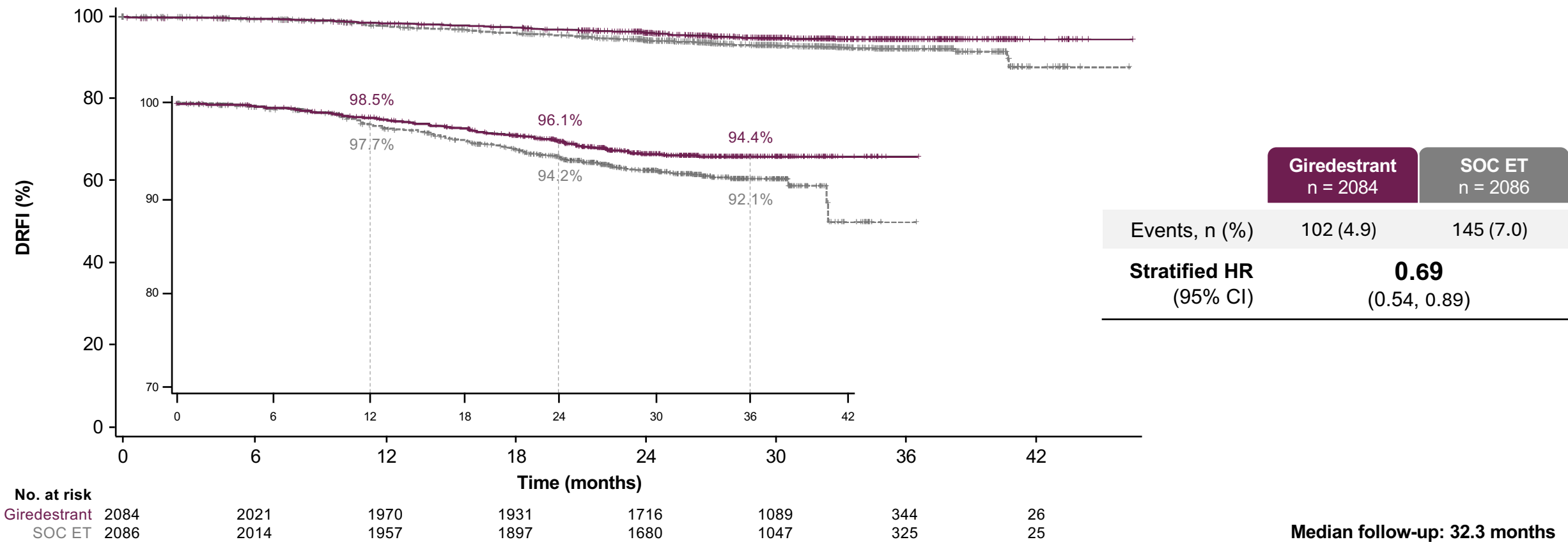
IdERA IDFS in Key Subgroups



IDFS benefit was consistent across key prespecified subgroups.

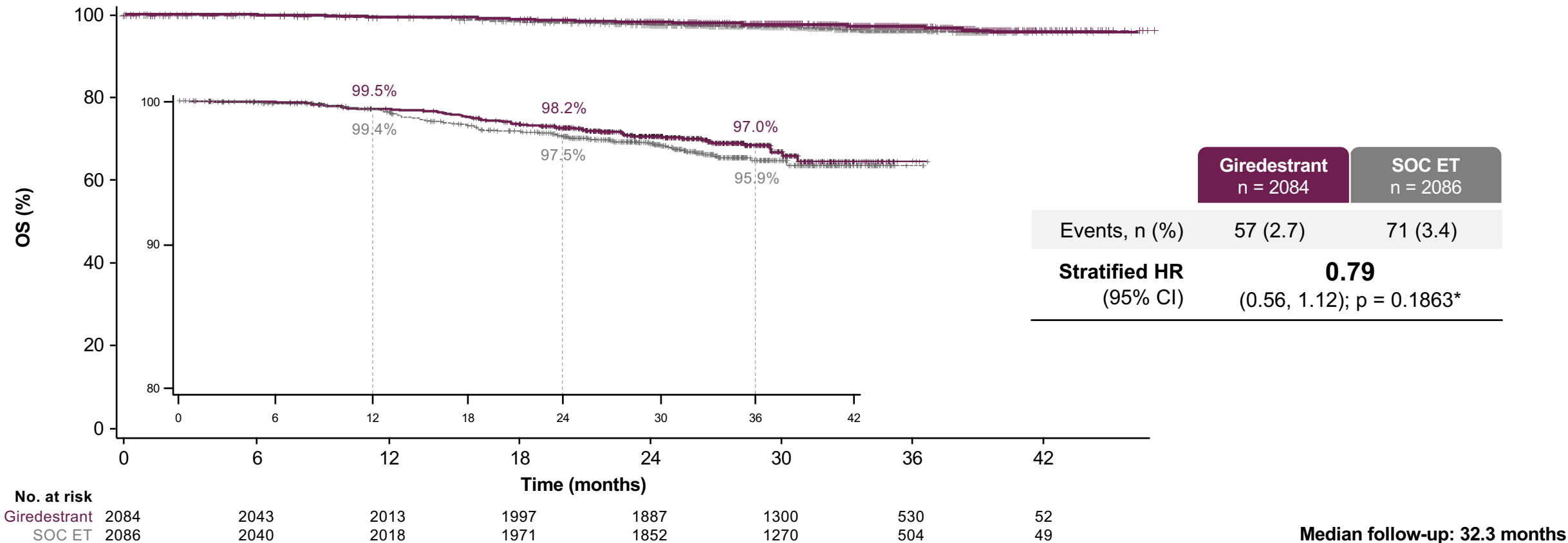
Data cutoff: August 8, 2025. HR estimates are unstratified. Median follow-up of 32.4 months in the giredestrant arm and 32.3 months in the SOC ET arm; maximum follow-up, 46.6 months and 46.3 months, respectively. One patient had Stage 0 disease (SOC ET arm); 26 had unknown Stage (18 in the giredestrant arm and eight in the SOC ET arm). AJCC, American Joint Committee on Cancer; CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; IDFS, invasive disease-free survival; SOC, standard-of-care.

lidERA: Distant Recurrence-free Interval



DRFI was improved vs SOC ET, with a 31% reduction in risk of developing metastatic disease.

lidERA: Interim Overall Survival



While OS data were immature, a clear positive trend was observed.
OS testing will continue at future analyses.

lidERA Safety Overview

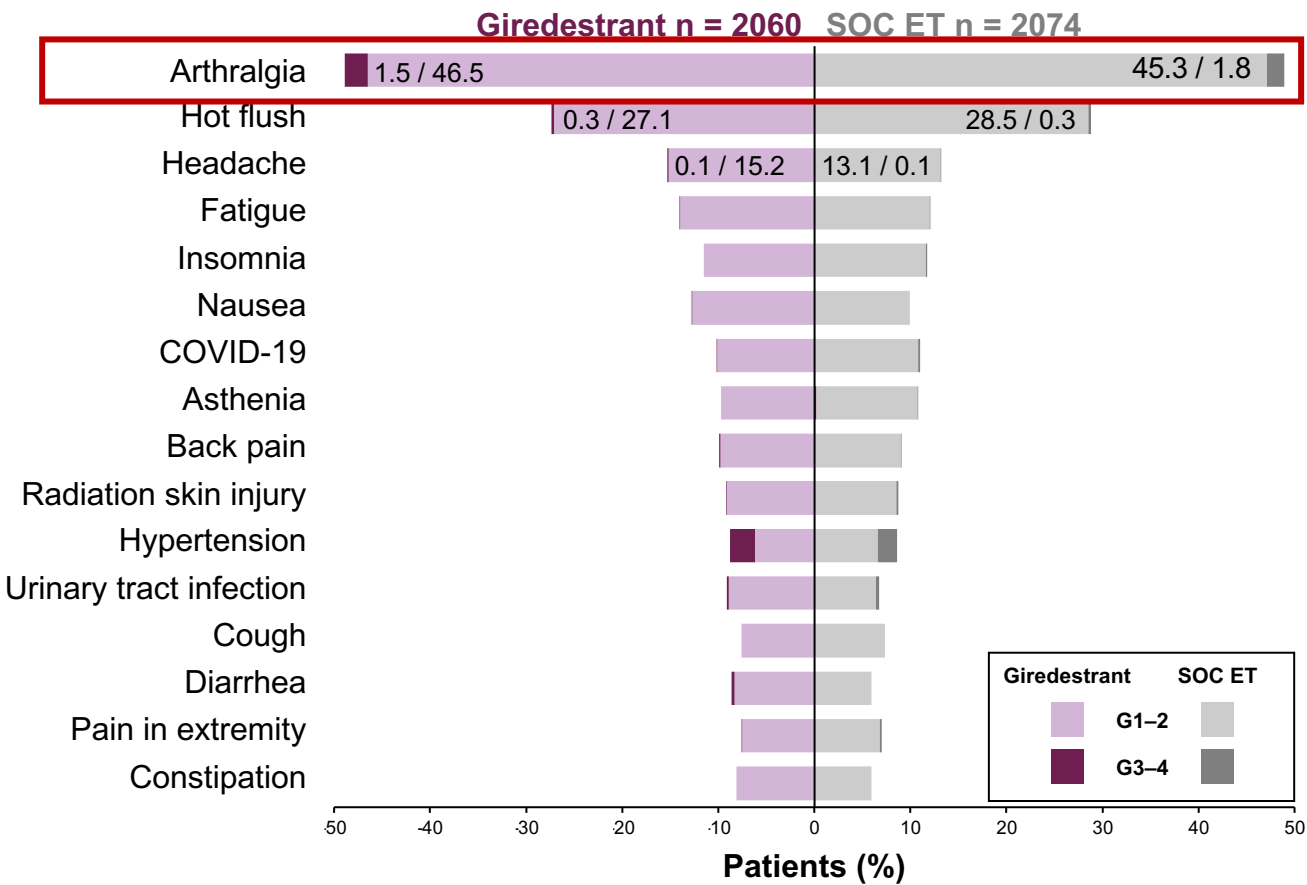
	Giredestrant n = 2060	SOC ET n = 2074
Median treatment duration, months (range)	31.64 (0.03–46.36)	30.88 (0.03–46.26)
Mean dose intensity, % (SD)	98.77 (3.07)	98.68 (3.73)
Patients with ≥ 1 AE, n (%)		
AEs (all grades)	1955 (94.9)	1957 (94.4)
TRAEs	1510 (73.3)	1498 (72.2)
AEs with fatal outcome*	6 (0.3)	16 (0.8)
TRAEs with fatal outcome	0	1 (< 0.1)
Grade 3–4 AEs†	407 (19.8)	372 (17.9)
Serious AEs	223 (10.8)	209 (10.1)
AEs leading to dose interruption	261 (12.7)	136 (6.6)
AEs leading to discontinuation from treatment	110 (5.3)	171 (8.2)

AEs, TRAEs, Grade 3–4 AEs, and serious AEs were comparable between treatment arms.

Data cutoff: August 8, 2025. * Giredestrant arm: Secondary cancers (colon and gastric); sepsis; gastrointestinal hemorrhage (n = 2); intestinal obstruction. SOC ET arm: Secondary cancers (pancreatic [n = 2], acute lymphocytic leukemia, bile duct, colon, gastric); sepsis (n = 1); cellulitis; endocarditis; gastrointestinal hemorrhage (n = 2); intestinal obstruction; death (n = 2); respiratory failure (n = 2); embolism; hypovolemic shock; acute myocardial infarction; hemophagocytic lymphohistiocytosis; acute kidney injury. † Most common Grade 3–4 AEs were hypertension (2.6% in the giredestrant arm vs 2.0% in the SOC ET arm) and arthralgia (1.5% vs 1.8%, respectively). AE, adverse event; ET, endocrine therapy; SD, standard deviation; SOC, standard-of-care; TRAE, treatment-related adverse event.

lidERA AE Overview

Common TEAEs (≥ 7.5% of patients in either arm at any grade)



Selected AEs

	Giredestrant n = 2060	SOC ET n = 2074
Patients, n (%) with treatment discontinuations due to AEs		
Musculoskeletal disorders	38 (1.8)	92 (4.4)
• Arthralgias (PT)	32 (1.6)	76 (3.7)
Vasomotor disorders	2 (< 0.1)	18 (0.9)
• Hot flush (PT)	1 (< 0.1)	16 (0.8)

	Giredestrant n = 2060			SOC ET n = 2074		
Patients, n (%) with selected AEs by medical concept*						
	G1	G2	G3–4	G1	G2	G3–4
Bradycardia [†]	217 (10.5)	15 (0.7)	0	64 (3.1)	2 (< 0.1)	0
Venous thromboembolic events	4 (0.2)	12 (0.6)	2 (< 0.1) [‡]	3 (0.1)	7 (0.3)	7 (0.3)

Data cutoff: August 8, 2025. * Assessed as medical concepts using grouped terms; all other AEs by medical concept were comparable between arms, including four patients per arm (0.2%) who experienced photopsia.† G2 events occurred in 17 patients; 13 resolved, four patients discontinued treatment and the events resolved. ‡ G3 only. AE, adverse event; ET, endocrine therapy; G, grade; PT, preferred term; SOC, standard-of-care; TEAE, treatment-emergent adverse event.

Efficacy and Safety of Giredestrant (GIRE) in Patients (pts) with Estrogen Receptor–Positive, HER2-Negative Early Breast Cancer (ER+, HER2– eBC) in the Phase III lidERA BC Clinical Trial: Results by Menopausal Status

Schmid P et al.

ASCO 2026;Abstract 502

Breast Cancer — Local/Regional/Adjuvant

SATURDAY MAY 30, 2026

Hall B1

1:39 PM – 1:51 PM CDT

lidERA Discussion

- Early data with decrease in events predominantly in higher risk patients; longer f/u needed to understand benefit in stage 1 population
- Question for how to integrate this into our practice upon approval since patients did not get concurrent CDK4/6i
- Possible recommendation:
 - ✓ **High Risk:** AI+ CDK4/6i
(maybe to be followed by sequential SERD in future)
 - ✓ **Intermediate Risk:** SERD
- Will concurrent SERD+ CDK4/6i be beneficial? Some data will come from CAMBRIA-2, and we will get safety data for giredestrant + CDK4/6i. Will this be enough?
- What about those intolerant to AI? Should we switch them to SERD?



CAMBRIA-2: Camizestrant vs SoC ET as Adjuvant Treatment^{1,2}

KEY ELIGIBILITY CRITERIA (N≈5500)

- Pre, peri or postmenopausal women or men
- ER+, HER2- EBC^a
- Up to 12 weeks of (neo)adjuvant ET prior to randomization
- Intermediate or high risk of recurrence

AI + abemaciclib capped at 30%
No ribociclib allowed

R
1:1

Standard ET (AI or tamoxifen)
± LHRH agonist^b
± abemaciclib (2 years)

7 YEARS



Camizestrant 75 mg QD
± LHRH agonist^b
± abemaciclib (2 years)

PRIMARY ENDPOINT
IBCFS

SECONDARY ENDPOINTS
IDFS, DRFS, OS, PRO,
Safety and tolerability, PK

Phase 3
Status: Recruiting
PCD: March 4, 2030
Sponsor: AstraZeneca

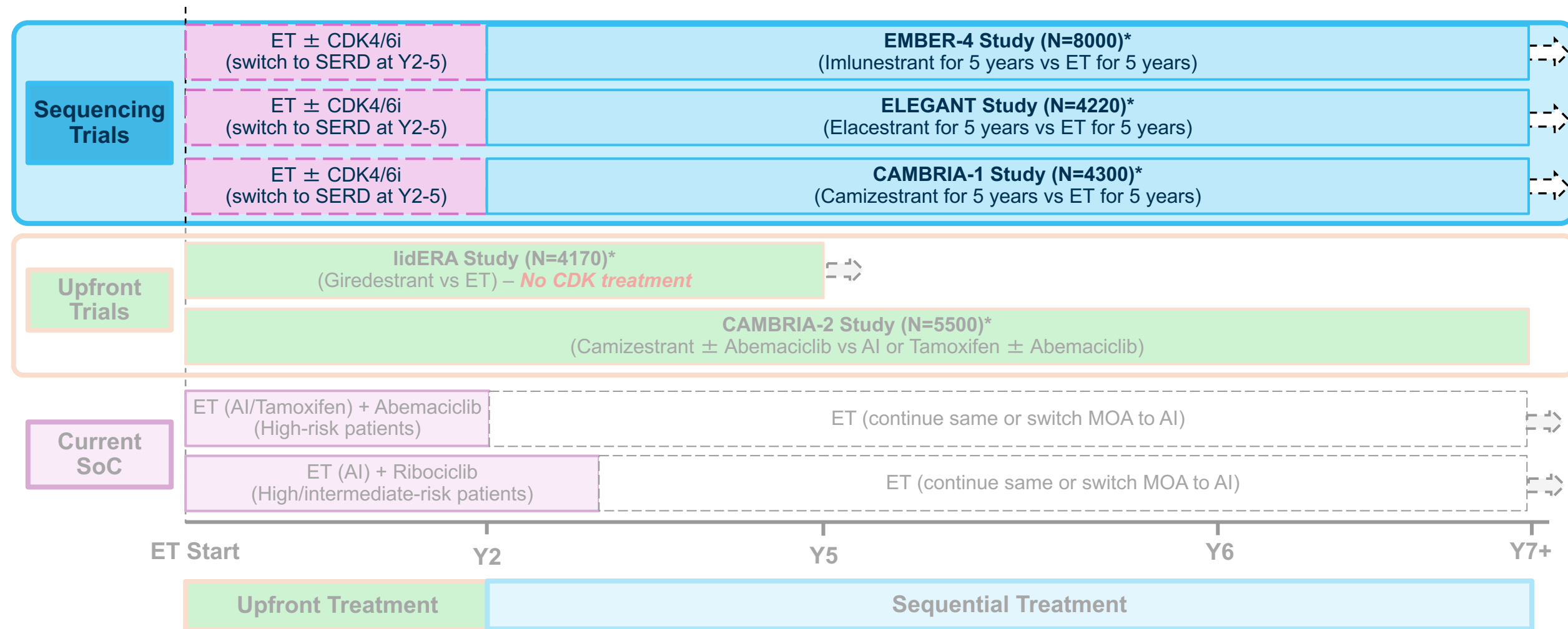
The CAMBRIA-2 study design presented aligns with clinical study protocol global amendment 1 v3 (20 May 2024).

^aER+: ER expression ≥10% of tumor cells; HER2-: IHC 0-1 positive and negative by ISH.

^bInvestigators' choice: AI (exemestane, letrozole, anastrozole) or tamoxifen, standard dose per investigator, once daily. Pre and perimenopausal female patients in both treatment arms will be administered an LHRH agonist.
AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DRFS, distant recurrence-free survival; EBC, early breast cancer; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IBCFS, invasive breast cancer-free survival; IDFS, invasive disease-free survival; IHC, immunohistochemistry; ISH, in situ hybridization; LHRH, luteinizing hormone-releasing hormone; mo, month; OS, overall survival; PCD, primary completion date; PK, pharmacokinetics; PRO, patient-reported outcomes; QD, once daily; R, randomized; SOC, standard of care.

1. <https://clinicaltrials.gov/study/NCT05952557>. (Accessed February 10, 2026). 2. Hamilton EP, et al. Future Oncol. 2025;21(7):795-806.

Overview of Ongoing Research in Adjuvant ET^{a,1-14}



EMBER-4: Study Design

Randomized, open-label, global, multicenter, phase 3 study (NCT05514054)

KEY ELIGIBILITY CRITERIA (N=8000)

- ER+, HER2- EBC
- Received 2–5 years of adjuvant ET ± CDK4/6i
- Increased risk of recurrence, defined as:
 - N2
 - N1 with ≥1 of below:
 - ✓ Histologic grade 3
 - ✓ Tumor size ≥5 cm
 - ✓ Tumor size >2 cm but <5 cm + grade 2
 - N0 with 1 of the below:
 - ✓ Tumor size ≥5 cm
 - ✓ Tumor size >2 cm but <5 cm + grade 3

R
1:1

Imlunestrant
400 mg/day

Stratification factors

- Time from initial adjuvant ET
- Prior adjuvant CDK4/6i therapy
- Nodal status
- Menopausal status
- Geographic region

Standard adjuvant ET
AI or tamoxifen

PRIMARY ENDPOINT

IDFS

(excluding 2nd non-breast primary)

SECONDARY ENDPOINTS

DRFS, OS, PRO, PK

Completed enrollment of **~8,000** patients following 2–5 years of adjuvant endocrine therapy
in the context of the established CDK4/6i standard of care.

AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; DRFS, distant recurrence-free survival; EBC, early breast cancer; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IDFS, invasive disease-free survival; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcomes; R, randomized. Jhaveri K, et al. Oral presentation at: SABCS 2025. Abstract GS3-08.

ELEGANT: Elacestrant vs SoC ET^{1,2}

KEY ELIGIBILITY CRITERIA (N=4220)

- Women or men
- Node-positive, ER+, HER2- EBC with high recurrence risk who received between 2–5 years of SoC ET ± CDK4/6i
- LHRH agonist will be administered for pre and perimenopausal women and men

R
1:1

Elacestrant
345 mg^a QD

5 YEARS



Continue ET^b
Anastrozole 1 mg QD, letrozole 2.5 mg QD, exemestane 25 mg QD, or tamoxifen 20 mg QD

PRIMARY ENDPOINT
IBCFS

KEY SECONDARY ENDPOINT
DRFS and OS

SECONDARY ENDPOINT
IDFS, Safety, PROs-QoL, and PK

PHASE 3

Status: Recruiting

PCD: August 2029

^aElacestrant 345 mg is equivalent to 400 mg elacestrant hydrochloride. ^bChange in ET after randomization in the control arm from an AI to another AI or to tamoxifen is allowed as per investigator's judgment. AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DRFS, distant relapse-free survival; EBC, early breast cancer; ER, endocrine receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IBCFS, invasive breast cancer-free survival; IDFS, invasive disease-free survival; LHRH, luteinizing hormone-releasing hormone; OS, overall survival; PCD, primary completion date; PK, pharmacokinetics; PRO, patient-reported outcome; QD, once daily; QoL, quality of life; SoC, standard of care. 1. <https://clinicaltrials.gov/study/NCT06492616>. (Accessed February 10, 2026). 2. Bardia A, et al. Poster presentation at: ASCO 2025. Abstract TPS619.

CAMBRIA-1: Extended Therapy with Camizestrant vs SoC ET^{1,2}

KEY ELIGIBILITY CRITERIA (N≈4300)

- Pre/peri/postmenopausal women or men
- ER+, HER2- EBC^a
- Receiving standard adjuvant ET for ≥2 and ≤5 years (+3 mo) with at least 5 years of remaining adjuvant ET planned
- May have received (neo)adjuvant CDK4/6i in combination with ET, but must have completed CDK4/6i portion of treatment
- Intermediate or high risk of recurrence

R
1:1

Continue standard ET
(AI or tamoxifen)
± LHRH agonist^b

5 YEARS



Camizestrant 75 mg QD
± LHRH agonist^b

PRIMARY ENDPOINT
IBCFS

SECONDARY ENDPOINT
IDFS, DRFS, OS, PRO,
Safety and tolerability, PK

PHASE 3

Status: Recruiting

PCD: April 20, 2027

The CAMBRIA-1 study design presented aligns with clinical study protocol global amendment 3 v4.0 (11 March 2024).

^aER+: ER expression ≥10% of tumor cells; HER2-: IHC 0–1 positive and negative by ISH.

^bInvestigators' choice: AI (exemestane, letrozole, anastrozole) or tamoxifen, standard dose per investigator, once daily. Pre and perimenopausal women, and men, will be administered an LHRH agonist.

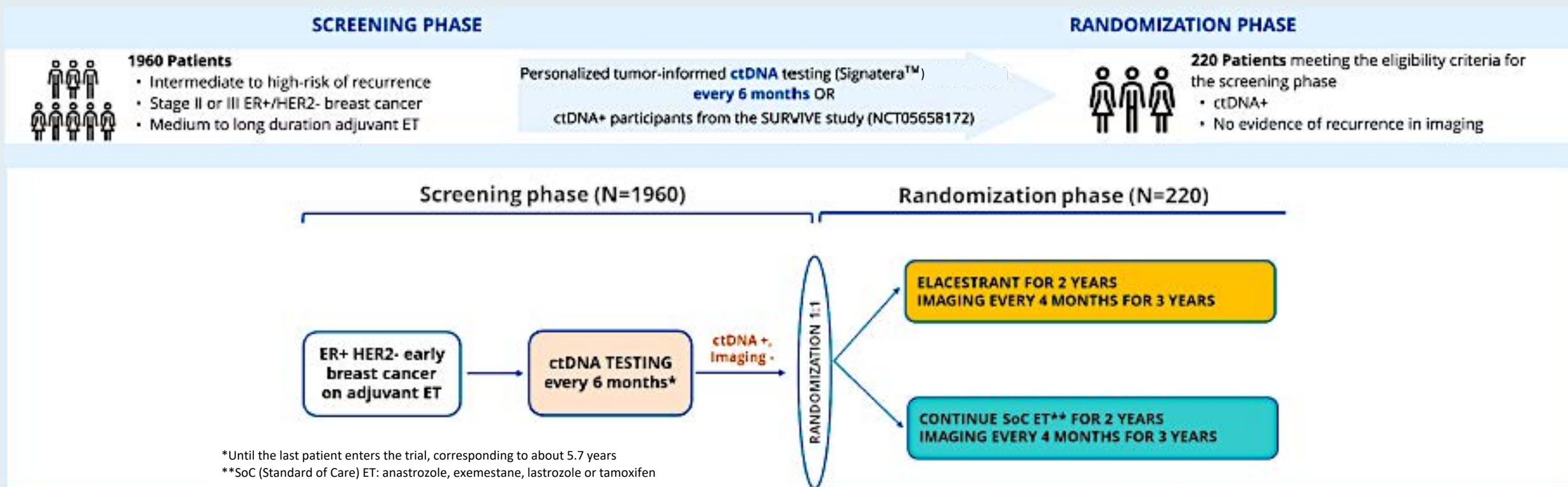
AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DRFS, distant recurrence-free survival; EBC, early breast cancer; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IBCFS, invasive breast cancer-free survival; IDFS, invasive disease-free survival; IHC, immunohistochemistry; ISH, in situ hybridization; LHRH, luteinizing hormone-releasing hormone; mo, month; OS, overall survival; PCD, primary completion date; PK, pharmacokinetics; PRO, patient-reported outcomes; QD, once daily; R, randomized; SoC, standard of care.

1. <https://clinicaltrials.gov/study/NCT05774951>. (Accessed February 10, 2026). 2. Hamilton EP, et al. Future Oncol. 2025;21(7):795-806.

Key Oral SERD Adjuvant Trials

Trial Name	N	Arms	Patient Population	Adjuvant CDK4/6i Allowed	Trial Identifier
CAMBRIA-2	5500	Camizestrant vs ET	High-risk ER+/HER2- first adjuvant therapy	Yes	NCT05952557
IdERA	4200	Giredestrant vs ET	Medium to high-risk ER+/HER2- first adjuvant therapy	No	NCT04961996
ELEGANT	4220	Elacestrant vs ET	High-risk ER+/HER2- 2-5y of adjuvant ET	Prior to trial entry	NCT06492616
EMBER-4	8000	Imlunestrant vs ET	High-risk ER+/HER2- 2-5y of adjuvant ET	Prior to trial entry	NCT05514054
CAMBRIA-1	4300	Camizestrant vs ET	Intermediate to high-risk ER+/HER2- 2-5y of adjuvant ET	Prior to trial entry	NCT05774951
TREAT ctDNA	220	Elacestrant vs ET	Elevated risk ER+/HER2- and ctDNA relapse 2-7y adjuvant ET	≥12 mo prior to trial entry	NCT05512364

TREAT ctDNA (EORTC-2129-BCG): A Phase III Trial of Elacestrant for Patients with ER-Positive, HER2-Negative Localized Breast Cancer with ctDNA Relapse



ctDNA = circulating tumor DNA

Would you like to have access to adjuvant giredestrant today for your patients with HR-positive localized breast cancer?

	Dr Hurvitz	Yes
	Dr Mayer	Yes
	Dr O'Shaughnessy	Yes
	Dr Tolaney	Yes
	Dr Turner	Yes
	Dr Kaklamani	Yes

Regulatory and reimbursement issues aside, for which specific populations would you be most inclined to employ adjuvant giredestrant?



Dr Hurvitz

All HR+/HER2-negative BC for which endocrine therapy is indicated



Dr Mayer

**Similar population to lidERA Breast Cancer
if not using CDK4/6 inhibitor**



Dr O'Shaughnessy

For pts who cannot tolerate AIs and for pts who are not CDK4/6i candidates who were eligible for lidERA Breast Cancer trial; as single-agent therapy after-completion of adjuvant CDK4/6i



Dr Tolaney

Would mostly use in Stage II cancers



Dr Turner

Stage II



Dr Kaklamani

Lower risk

If giredestrant were available, regulatory and reimbursement issues aside, what would you generally recommend for patients who meet the criteria for both an adjuvant CDK4/6 inhibitor and adjuvant giredestrant?



Dr Hurvitz

CDK4/6i combined w/ ET for the initial 2 to 3 years, then switch to giredestrant



Dr Mayer

CDK4/6i combined w/ ET for the initial 2 to 3 years, then switch to giredestrant



Dr O'Shaughnessy

CDK4/6i combined w/ ET for the initial 2 to 3 years, then switch to giredestrant



Dr Tolaney

CDK4/6i combined w/ ET for the initial 2 to 3 years, then switch to giredestrant



Dr Turner

CDK4/6 inhibitor



Dr Kaklamani

CDK4/6i combined w/ ET for the initial 2 to 3 years, then switch to giredestrant

How would you indirectly compare the global tolerability (ie, rates and severity of arthralgias, hot flashes and other side effects) of adjuvant giredestrant to that of standard adjuvant endocrine therapy for patients with HR-positive localized breast cancer?



Dr Hurvitz

Adjuvant giredestrant is more tolerable



Dr Mayer

Adjuvant giredestrant is more tolerable



Dr O'Shaughnessy

Adjuvant giredestrant is more tolerable



Dr Tolaney

Adjuvant giredestrant is more tolerable



Dr Turner

About the same



Dr Kaklamani

Adjuvant giredestrant is more tolerable

If adjuvant giredestrant were available, would you consider switching to that strategy for a patient with HR-positive localized breast cancer who was receiving standard adjuvant endocrine therapy but having difficulty with tolerability?



Dr Hurvitz

Yes



Dr Mayer

Yes



Dr O'Shaughnessy

Yes



Dr Tolaney

Yes



Dr Turner

Yes



Dr Kaklamani

Yes

**What Clinicians Want to Know: Addressing Community
Oncologists' Questions About the Current and Future Role of
Antibody-Drug Conjugates in the Management of Breast Cancer**
A CME Symposium Held Adjunct with the 2026 ASCO® Annual Meeting

Monday, June 1, 2026

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Professor Giuseppe Curigliano, MD, PhD

Rebecca A Dent, MD, MSc

Erika Hamilton, MD

Nadia Harbeck, MD, PhD

Moderator

Hope S Rugo, MD

Second Opinion: Investigators Provide Perspectives on the Current and Future Use of Novel Therapies for Non-Hodgkin Lymphoma

A CME Symposium Held Adjunct with the 2026 ASCO® Annual Meeting

Monday, June 1, 2026

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Christopher Flowers, MD, MS, FASCO

Matthew Lunning, DO

Sonali M Smith, MD

Moderator

Brad S Kahl, MD

**Consensus or Controversy? Documenting
and Discussing Investigators' Approaches to the
Management of Relapsed/Refractory Multiple Myeloma**

Monday, June 1, 2026

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Melissa Alsina, MD

Hans Lee, MD

Paul G Richardson, MD

Moderator

Sagar Lonial, MD, FACP, FASCO

Thank you for joining us!
Your feedback is very important to us.

Please complete the survey currently up on the iPads for attendees in the room and on Zoom for those attending virtually. The survey will remain open up to 5 minutes after the meeting ends.

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In-person attendees: Please refer to the program syllabus for the CME credit link or QR code. Online/Zoom attendees: The CME credit link is posted in the chat room.