



Multidisciplinary Approaches to Cancer Symposium

New Approaches to the Treatment of HR Positive Early and Advanced-stage Breast Cancer

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City of Hope

Disclosures

- Consultant for AstraZeneca, BioNTech, Daiichi Sankyo, Gilead, Menarini Stemline, Novartis, and Pfizer
- Grant/Research Support from Merck

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.



Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Discuss possible barriers and biases which may impact patient care.*
- *Highlight that all populations may benefit from recent advances in HR+ breast cancer*



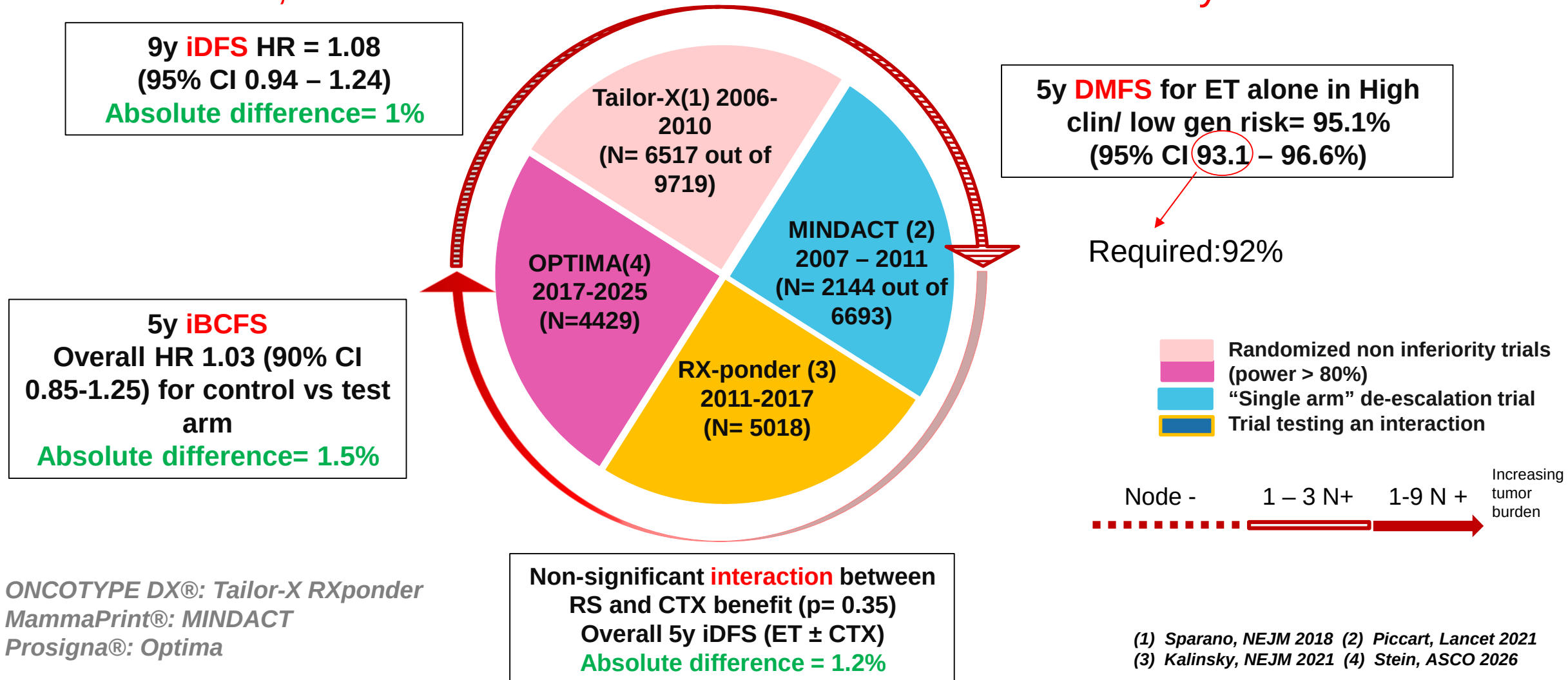
Overview: Early Stage

- Molecular risk assessment and Prosigna
- Review of updates with adjuvant CDK4/6i
 - monarchE: Primary OS results,
 - menopausal status and other subgroups
 - NATALEE: 5-year update,
 - Intrinsic subtype analysis
- Adjuvant oral SERD
 - lidERA Breast Cancer,
 - menopausal status

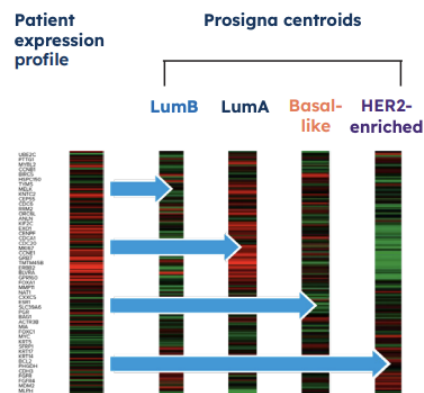


Endocrine therapy (ET) NOT INFERIOR to ET + Chemotherapy in the presence of a favorable multigene expression assay*

N = 18,108 women recruited in 4 academic trials over 25 years



What is Prosigna



Nodal Status

Node 0
Node 1-3

Gross Tumour size

<2cm
≥2cm

Prosigna® Score =

aR_{LumA} +

bR_{LumB} +

cR_{Her2e} +

dR_{Basal} +

Pearson's
correlation
to centroids

eP +

fT

Proliferation
score & Gross
tumour size

Patient Report



2nd GENERATION ASSAY Prosigna®

- 50 genes
- Gene expression + clinical factors (age, node status, tumor size, histologic grade)
- Results can be available in as little as 24 hours

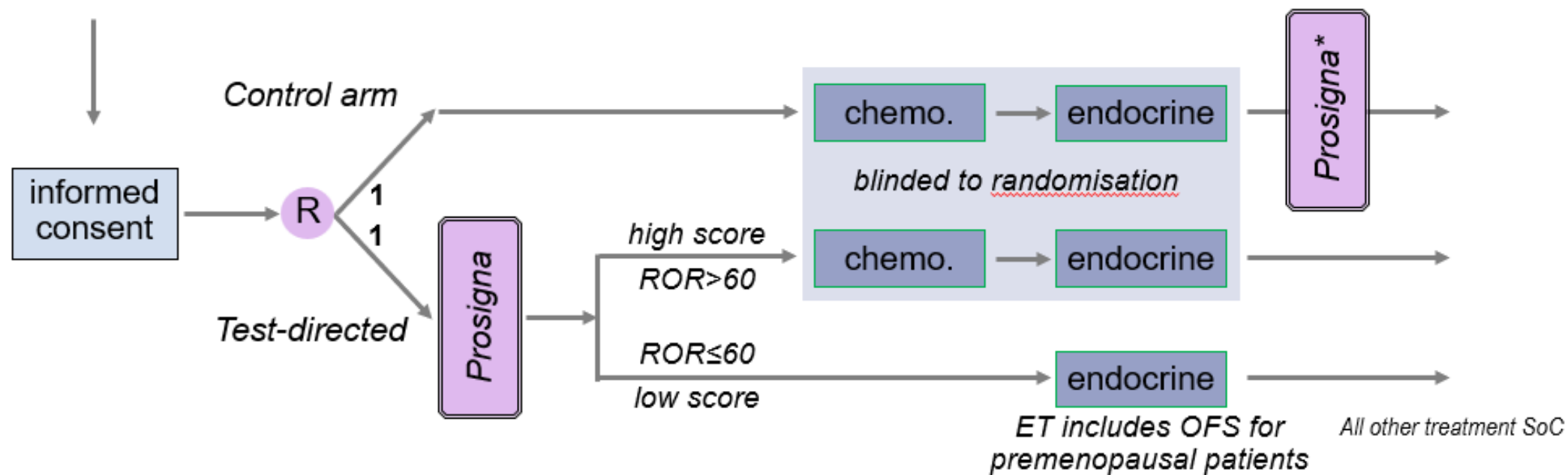
10-YEAR PROGNOSIS

OPTIMA design

Main eligibility criteria

- Women & men age ≥ 40 with excised breast cancer
- ER-pos (IHC $>10\%$) & HER2-neg

- Nodes: $\triangleright 0-9N+$,
 $\triangleright$ minimum T-size requirement if $N0/ N1mi$
- Neoadjuvant chemotherapy prohibited



*Control arm Prosigna testing used for analysis only. U.K. control arm testing performed following recruitment completion

Patient and tumor characteristics

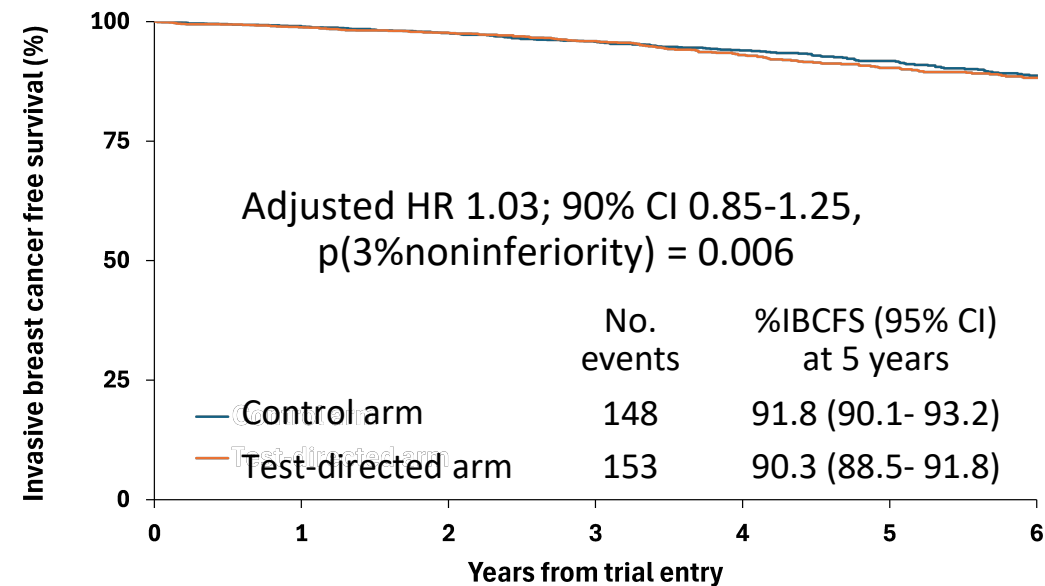
Characteristic	Control arm	Test directed arm	Total
number PP	2059	2094	4153
age (range)	55 (40-84)	56 (40-82)	56 (40-84)
premenopausal	776 (38%)	775 (37%)	1551 (37%)
postmenopausal	1265 (61%)	1302 (62%)	2567 (62%)
men	18 (1%)	17 (1%)	35 (1%)
grade 1-2	1417 (69%)	1465 (70%)	2862 (69%)
grade 3	642 (31%)	629 (30%)	1271 (31%)
tumor size <30 mm	1104 (54%)	1128 (54%)	2232 (54%)
tumor size ≥30 mm	955 (46%)	966 (46%)	3050 (46%)
<u>nodes</u> : 0 / micromets	160 (8%)	167 (8%)	327 (8%)
1-3*	1515 (74%)	1534 (73%)	3049 (73%)
4-9	384 (18%)	393 (19%)	777 (19%)

*39% of pN1 tumors had a sentinel node biopsy only



Invasive Breast Cancer Free Survival

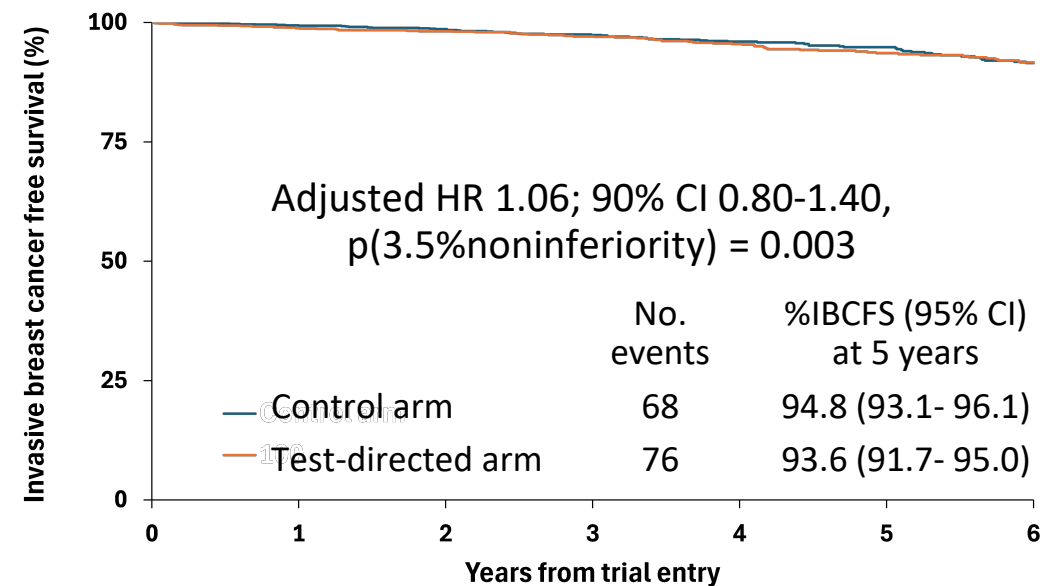
Complete Per Protocol population



Number at risk:							
Control	2059	1818	1563	1283	999	741	485
Test-directed	2094	1857	1591	1303	989	724	481

Demonstrated non-inferiority limit = 2%
No certainty of chemotherapy benefit
1.5% observed 5-year difference –favors chemotherapy

ROR ≤60 subpopulation



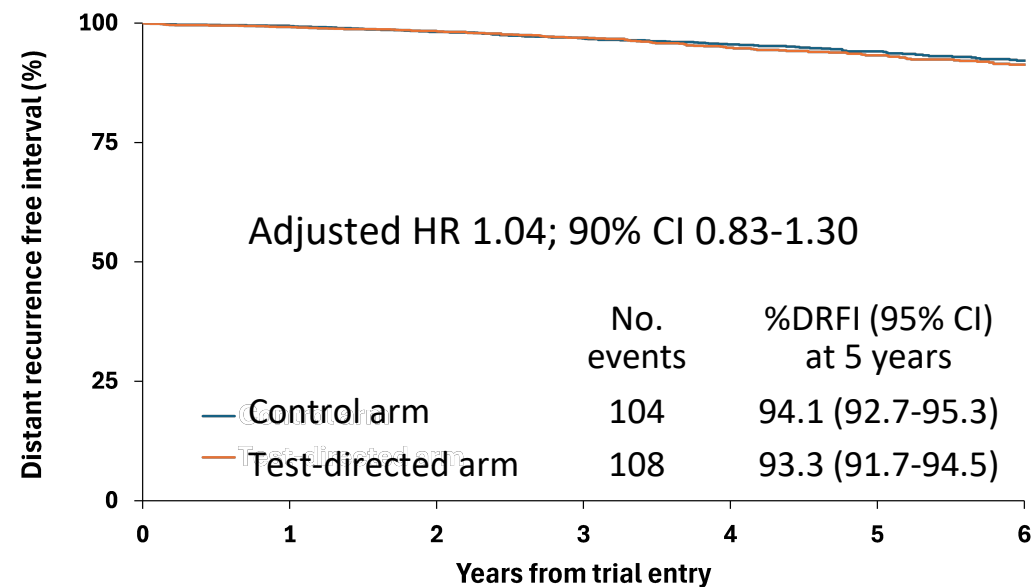
Number at risk:							
Control	1358	1207	1043	862	672	504	337
Test-directed	1421	1257	1086	905	694	503	342

Demonstrated non-inferiority limit = 2%
No certainty of chemotherapy benefit
1.2% observed 5-year difference –favors chemotherapy



Distant Recurrence Free Interval

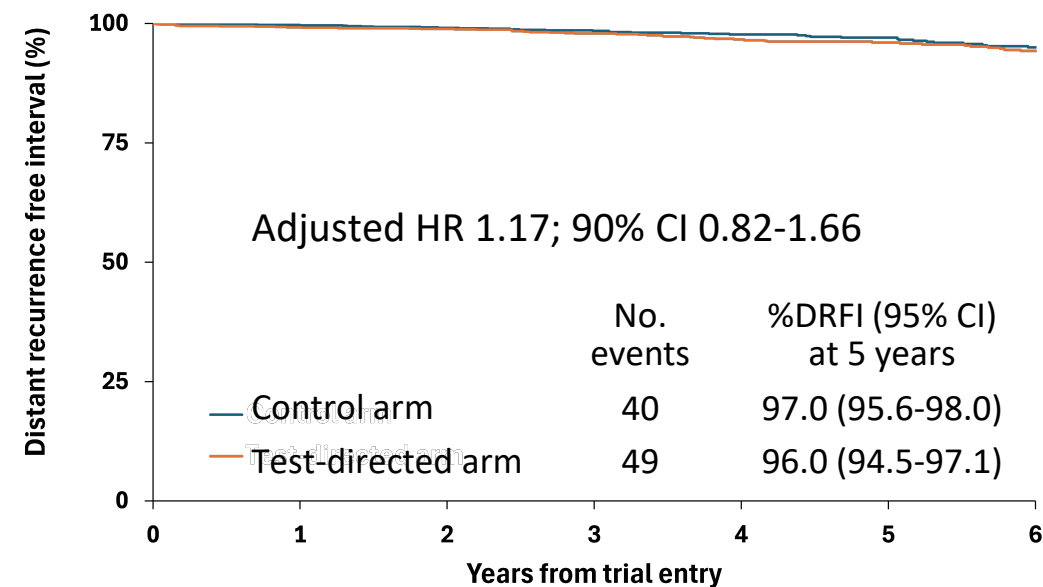
Complete Per Protocol population



Number at risk:							
Control	2059	1822	1568	1286	1004	746	489
Test-directed	2094	1863	1599	1311	993	732	487

0.8% observed 5-year difference –favors chemotherapy

ROR ≤60 subpopulation

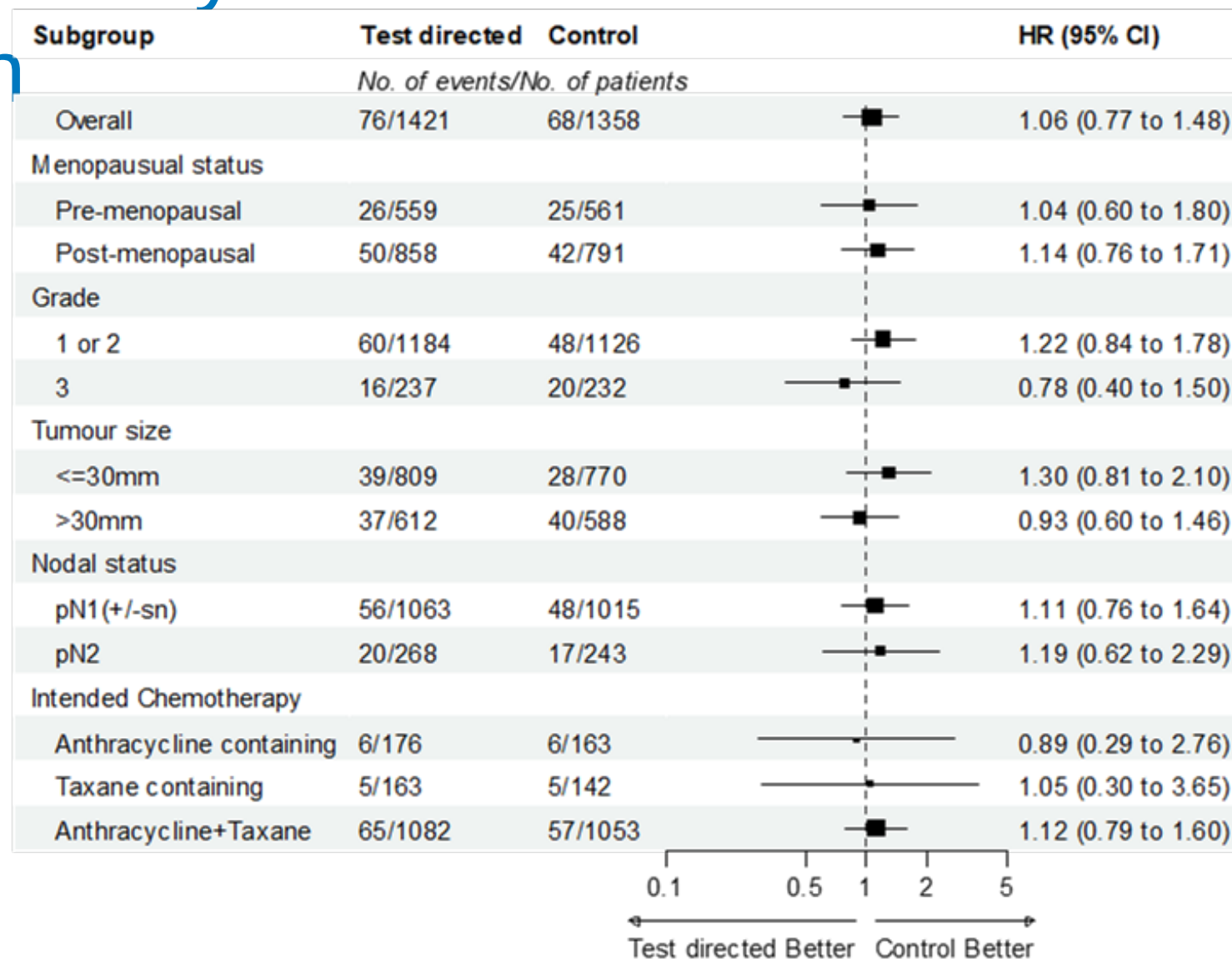


Number at risk:							
Control	1358	1209	1046	865	676	507	340
Test-directed	1421	1262	1093	911	696	509	346

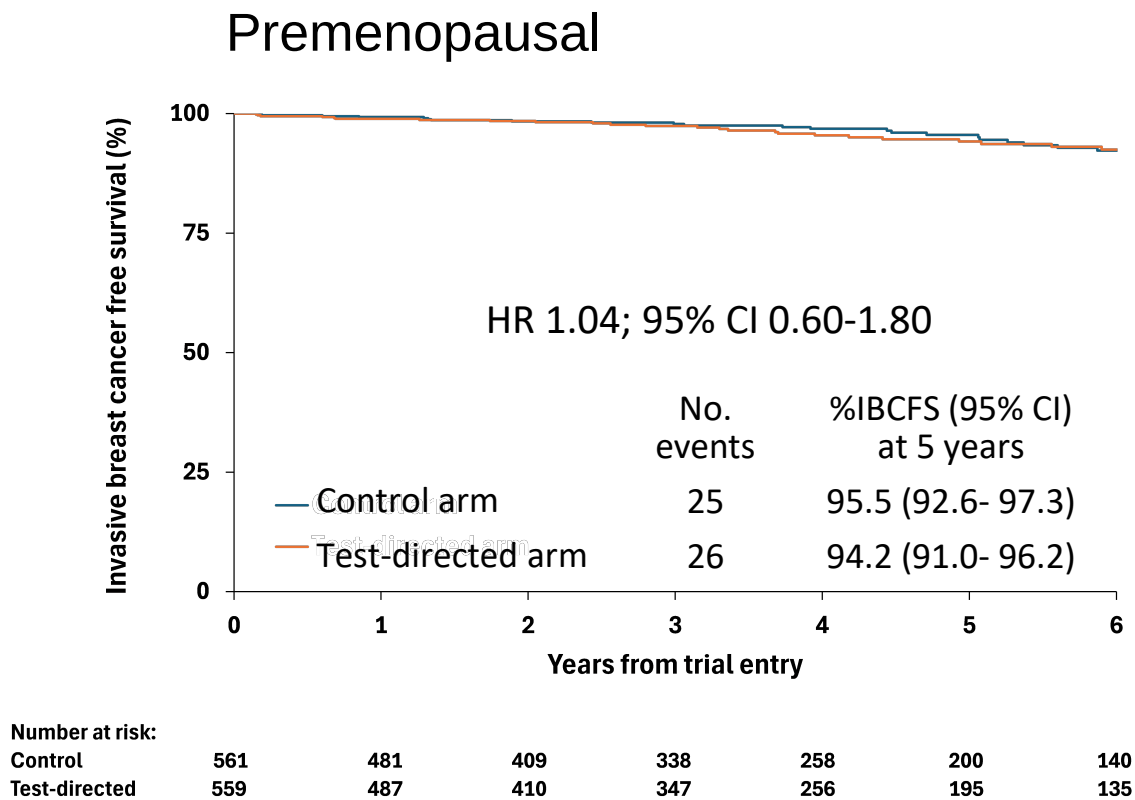
1.0% observed 5-year difference –favors chemotherapy



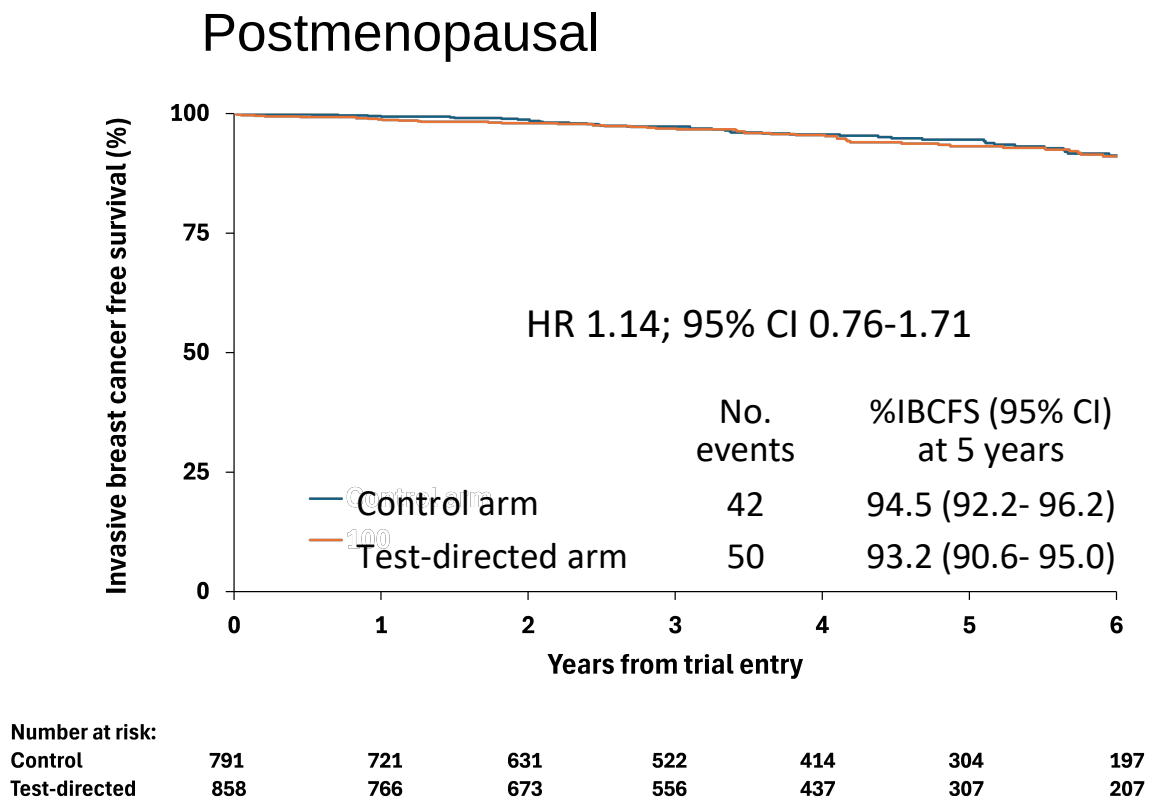
Subgroup analysis: low ROR score population



IBCFS vs menopausal status: low ROR score population



1.3% observed 5-year difference -favors chemotherapy

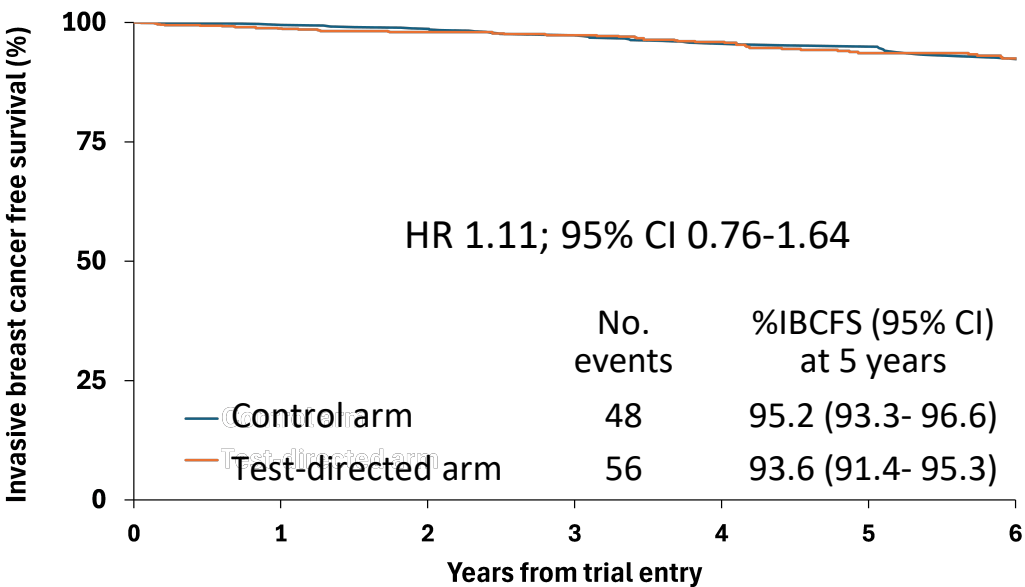


1.3% observed 5-year difference -favors chemotherapy



IBCFS vs nodal status: low ROR score population

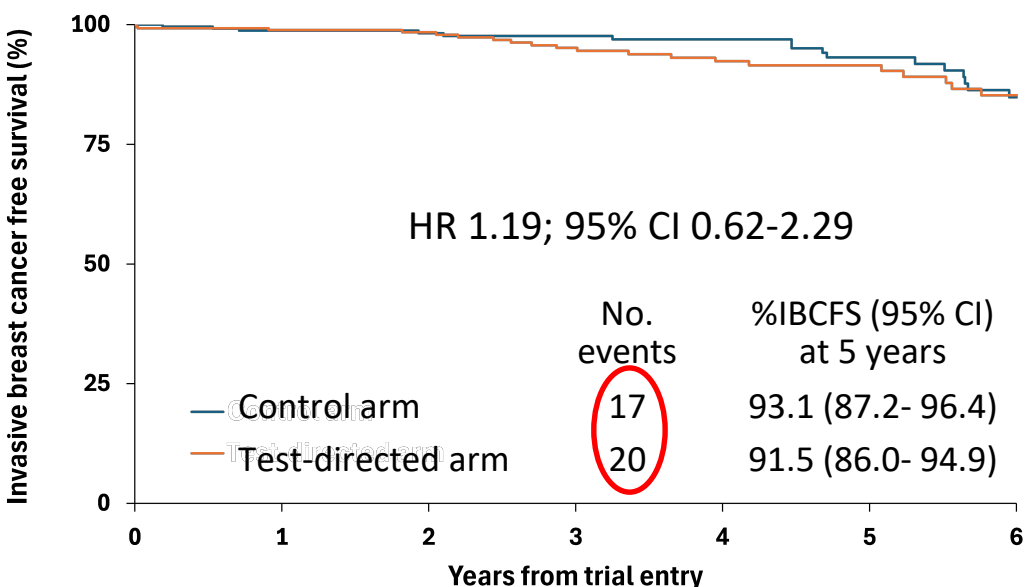
1-3 involved nodes



Number at risk:							
Control	1015	914	798	651	499	382	264
Test-directed	1063	953	829	700	539	389	270

1.6% observed 5-year difference -favors chemotherapy

4-9 involved nodes



Number at risk:							
Control	243	214	181	155	125	84	48
Test-directed	269	232	197	158	118	86	49

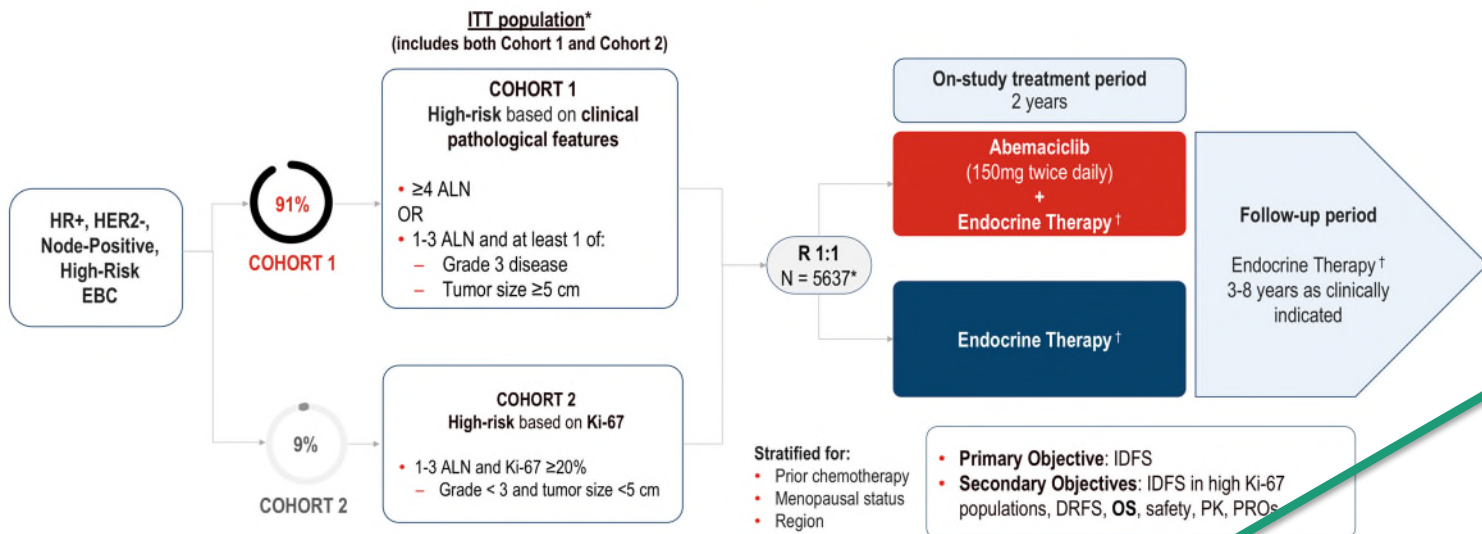
1.6% observed 5-year difference -favors chemotherapy



Where do we stand?

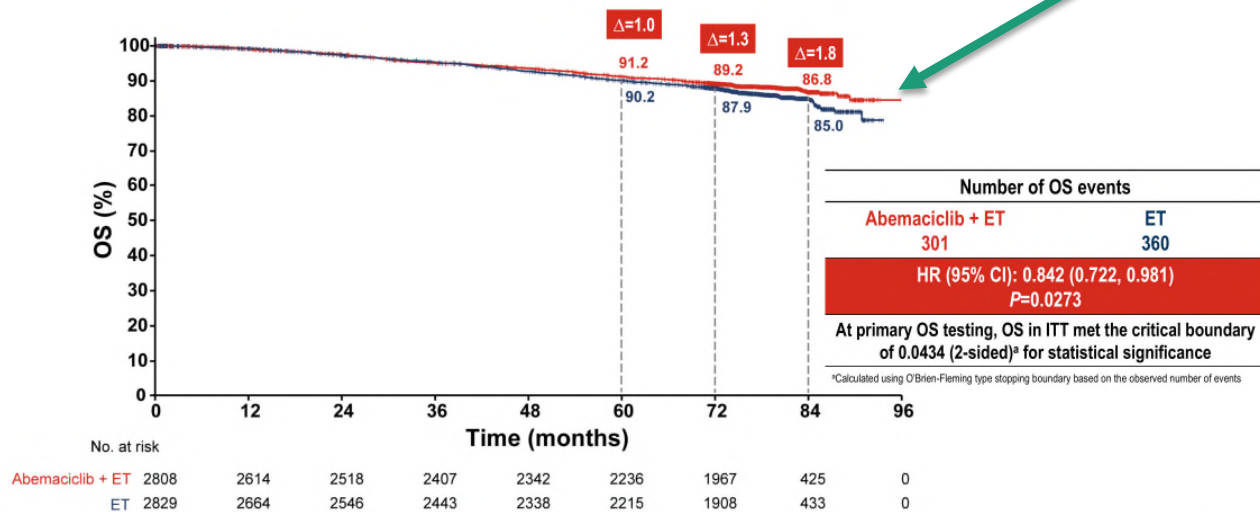
- **Limitations:**
 - majority of patients have not reached 5 years of follow up
 - Women <40 years were not included
 - Not a diverse population
- **OPTIMA has demonstrated that the 50-gene Prosigna test identifies a patient group with minimal if any chemotherapy benefit**
 - Premenopausal patients age >40
 - Larger tumor size
 - 4-9 Lymph nodes???

monarchE Trial Design (NCT03155997)



1.8% = 15.8% Rel Risk Reduction

Key Secondary Endpoint: Overall Survival in ITT



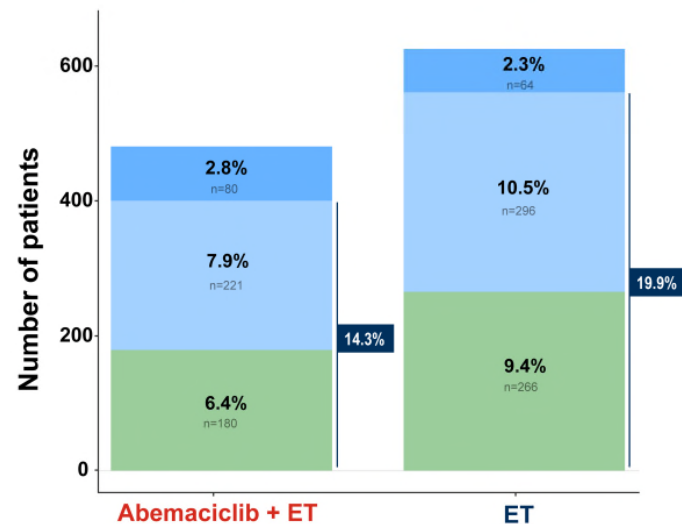
At a median follow-up of 6.3 years, abemaciclib + ET reduced the risk of death by 15.8% compared to ET alone

Consistent OS Benefit Across Prespecified Subgroups

	Abemaciclib + ET		ET				
	n	Events	n	Events		HR (95% CI)	Interaction p-value
Overall*	2808	301	2829	360		0.842 (0.722, 0.981)	
Age, years							0.786
<65	2371	233	2416	283		0.825 (0.694, 0.982)	
≥ 65	437	68	413	77		0.870 (0.628, 1.205)	
Menopausal status							0.163
Premenopausal	1221	91	1232	123		0.716 (0.546, 0.939)	
Postmenopausal	1587	210	1597	237		0.907 (0.753, 1.092)	
Prior treatment							0.433
Neoadjuvant chemotherapy	1039	143	1048	180		0.788 (0.633, 0.982)	
Adjuvant chemotherapy	1642	142	1647	159		0.892 (0.712, 1.119)	
Baseline ECOG PS							0.577
0	2405	252	2369	298		0.822 (0.695, 0.972)	
1	401	48	455	61		0.927 (0.635, 1.353)	
Primary tumor size, mm							0.072
<20	781	55	767	87		0.598 (0.427, 0.839)	
≥ 20 but < 50	1371	150	1419	178		0.880 (0.708, 1.093)	
≥ 50	607	91	610	91		1.001 (0.748, 1.339)	
No. of positive lymph nodes							0.531
1-3	1118	96	1142	109		0.893 (0.679, 1.175)	
4-9	1107	110	1126	134		0.841 (0.653, 1.082)	
10 or more	575	92	554	117		0.723 (0.550, 0.950)	
Tumor grade							0.732
Grade 1	209	16	216	21		0.788 (0.411, 1.510)	
Grade 2	1377	146	1395	158		0.930 (0.743, 1.165)	
Grade 3	1086	134	1064	157		0.829 (0.658, 1.044)	
Tumor stage							0.516
Stage II	716	50	740	69		0.746 (0.518, 1.073)	
Stage III	2078	248	2077	289		0.850 (0.717, 1.007)	
First ET							0.366
Tamoxifen	857	73	898	102		0.734 (0.543, 0.991)	
Aromatase inhibitor	1931	226	1887	257		0.864 (0.723, 1.033)	

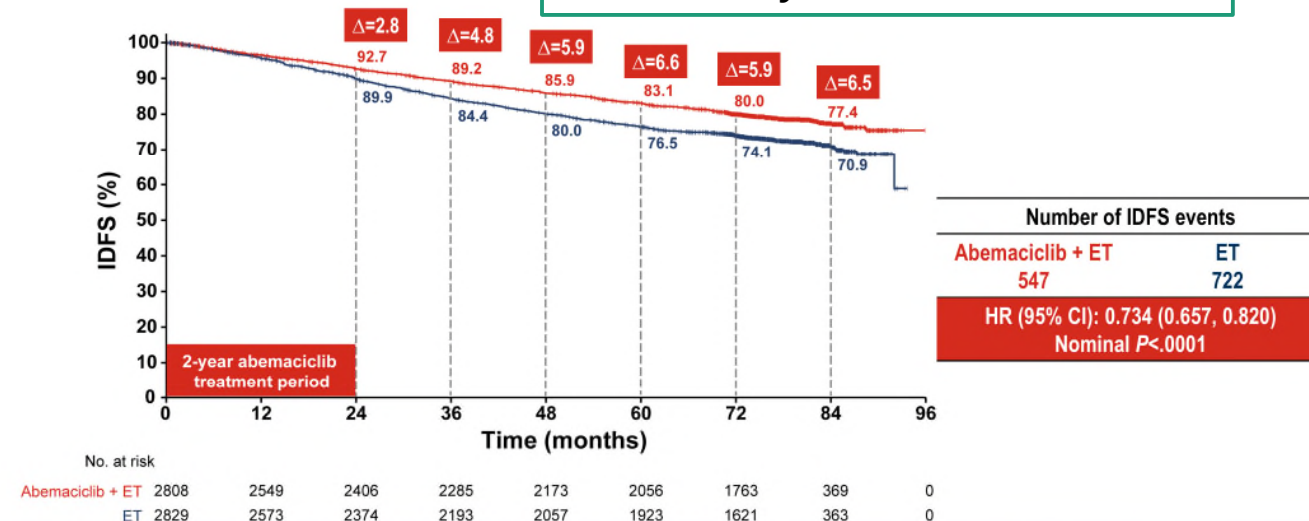
*Region of enrollment, race, and progesterone status data not shown due to space limitations

~30% Fewer Patients in Abemaciclib Arm Living with Metastatic Disease



Status ■ Deaths not related to breast cancer* ■ Deaths due to breast cancer ■ Alive with metastatic disease

iDFS benefit sustained over time
6.5% at 7 years



Abemaciclib + ET reduced the risk of IDFS events by 26.6% compared to ET alone

Consistent IDFS Benefit Across Prespecified Subgroups

	Abemaciclib + ET		ET			
	n	Events	n	Events	HR (95% CI)	Interaction p-value
Overall*	2808	547	2829	722	0.734 (0.657, 0.820)	
Age, years						0.227
<65	2371	440	2416	600	0.711 (0.629, 0.804)	
≥65	437	107	413	122	0.847 (0.653, 1.098)	
Menopausal status						0.225
Premenopausal	1221	207	1232	286	0.676 (0.565, 0.808)	
Postmenopausal	1587	340	1597	436	0.778 (0.675, 0.896)	
Prior treatment						0.506
Neoadjuvant chemotherapy	1039	258	1048	350	0.695 (0.592, 0.816)	
Adjuvant chemotherapy	1642	257	1647	336	0.746 (0.634, 0.877)	
Baseline ECOG PS						0.162
0	2405	457	2369	601	0.713 (0.631, 0.805)	
1	401	90	455	120	0.879 (0.669, 1.156)	
Primary tumor size, mm						0.078
<20	781	110	767	170	0.606 (0.477, 0.771)	
≥20 but <50	1371	285	1419	351	0.804 (0.705, 0.963)	
≥50	607	141	610	193	0.685 (0.551, 0.851)	
No. of positive lymph nodes						0.724
1-3	1118	174	1142	227	0.765 (0.628, 0.932)	
4-9	1107	198	1126	285	0.682 (0.569, 0.818)	
10 or more	575	172	554	209	0.720 (0.589, 0.881)	
Tumor grade						0.817
Grade 1	209	31	216	47	0.668 (0.424, 1.051)	
Grade 2	1377	259	1395	344	0.731 (0.622, 0.859)	
Grade 3	1085	232	1064	284	0.776 (0.653, 0.923)	
Tumor stage						0.097
Stage II	716	100	740	133	0.768 (0.592, 0.995)	
Stage III	2078	444	2077	585	0.722 (0.638, 0.817)	
First ET						0.177
Tamoxifen	857	156	866	234	0.652 (0.532, 0.798)	
Aromatase inhibitor	1931	389	1987	485	0.768 (0.672, 0.878)	

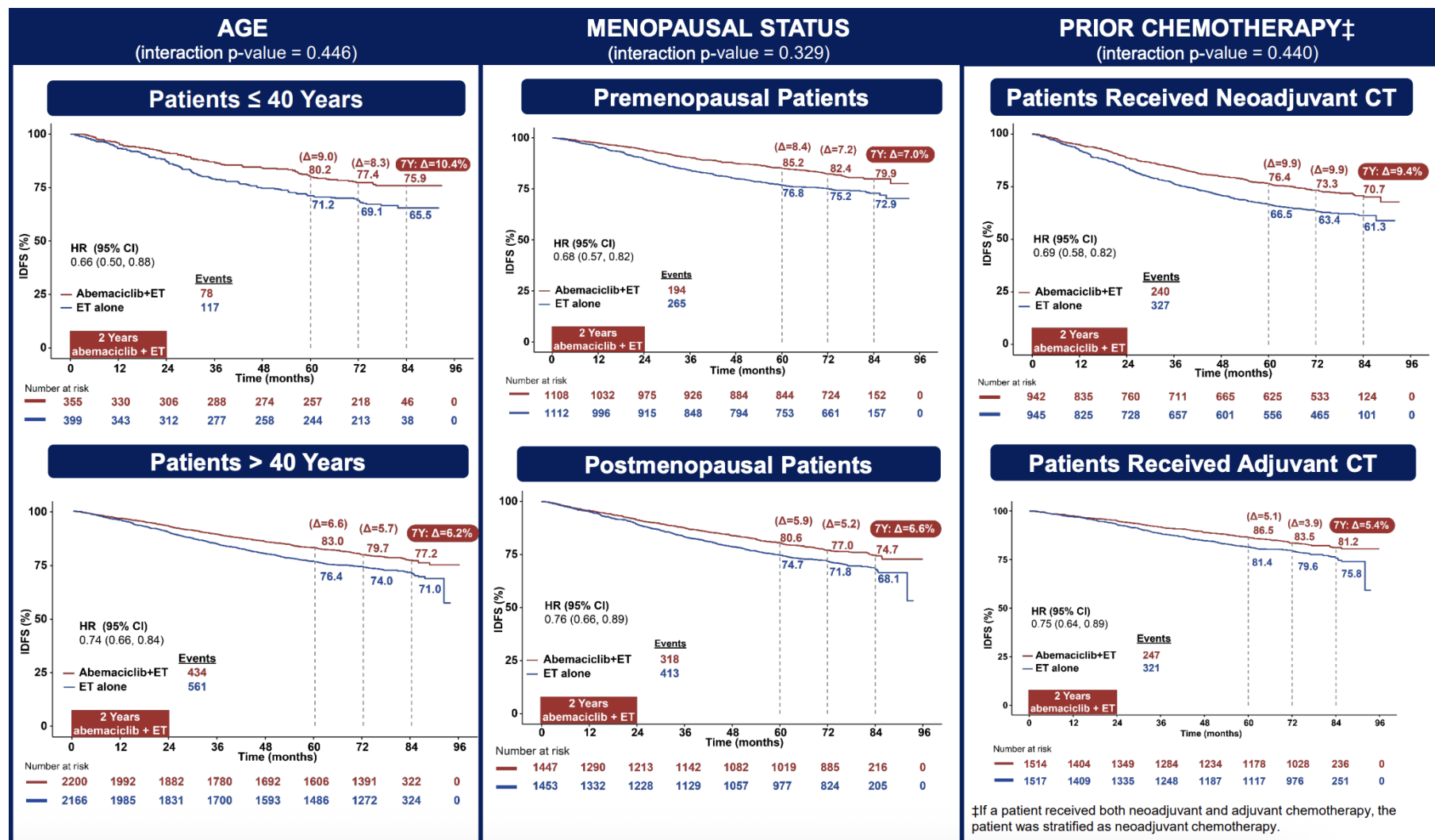
*Region of enrollment, race, and progesterone status data not shown due to space limitations

Most IDFS Events Were Distant Metastatic Disease

	Abemaciclib + ET N=2808	ET N=2829
Distribution of first recurrence in ITT population, n (%)	505 (18.0)	693 (24.5)
Type of recurrence event		
Distant recurrence	381 (13.6)	523 (18.5)
Local/regional recurrence	70 (2.5)	109 (3.9)
Second primary neoplasm	48 (1.7)	52 (1.8)
Contralateral breast cancer	14 (0.5)	22 (0.8)
Site of initial distant recurrence		
Bone	166 (5.9)	265 (9.4)
Liver	99 (3.5)	133 (4.7)
Lung	69 (2.5)	76 (2.7)
Brain/Central Nervous System	32 (1.1)	31 (1.1)
Lymph node	29 (1.0)	46 (1.6)
Pleura	8 (0.3)	28 (1.0)

Abemaciclib + ET reduced the number of patients with metastases at common sites
Low rates of second primary neoplasms were observed in both arms

monarchE Cohort 1 IDFS benefit by key clinical subgroups

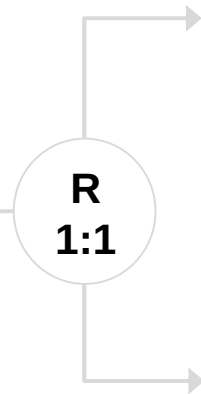


Study Design: NATALEE

An open-label, multicenter, randomized, phase 3 trial^{1,2}

Adult patients with stage II and III HR+/HER2- EBC

- Prior ET allowed up to 12 months
- **Anatomical stage IIA^a**
 - N0 with:
 - Grade 2 and evidence of high risk:
 - Ki-67 $\geq$ 20%
 - Oncotype DX Breast Recurrence Score $\geq$ 26 or
 - High risk via genomic risk profiling
 - Grade 3
 - N1
- **Anatomical stage IIB^a**
 - N0 or N1
- **Anatomical stage III**
 - N0, N1, N2, or N3



RIB
400 mg/day
3 weeks on/1 week off for 3 y
+
NSAI
Letrozole or anastrozole^b for $\geq$ 5 y
+ goserelin in men and premenopausal women

NSAI
Letrozole or anastrozole^b for $\geq$ 5 y
+ goserelin in men and premenopausal women

Primary End Point
iDFS using STEEP criteria

Secondary End Points

- RFS, DDFS, OS
- PROs
- Safety and tolerability
- PK

Exploratory End Points

- DRFS
- Gene expression and alterations in tumor ctDNA/ctRNA samples

Efficacy outcomes for the 5-year analysis were estimated by the Kaplan-Meier method, and results are descriptive. The Cox proportional hazards model was used to estimate the HRs and 95% CIs.



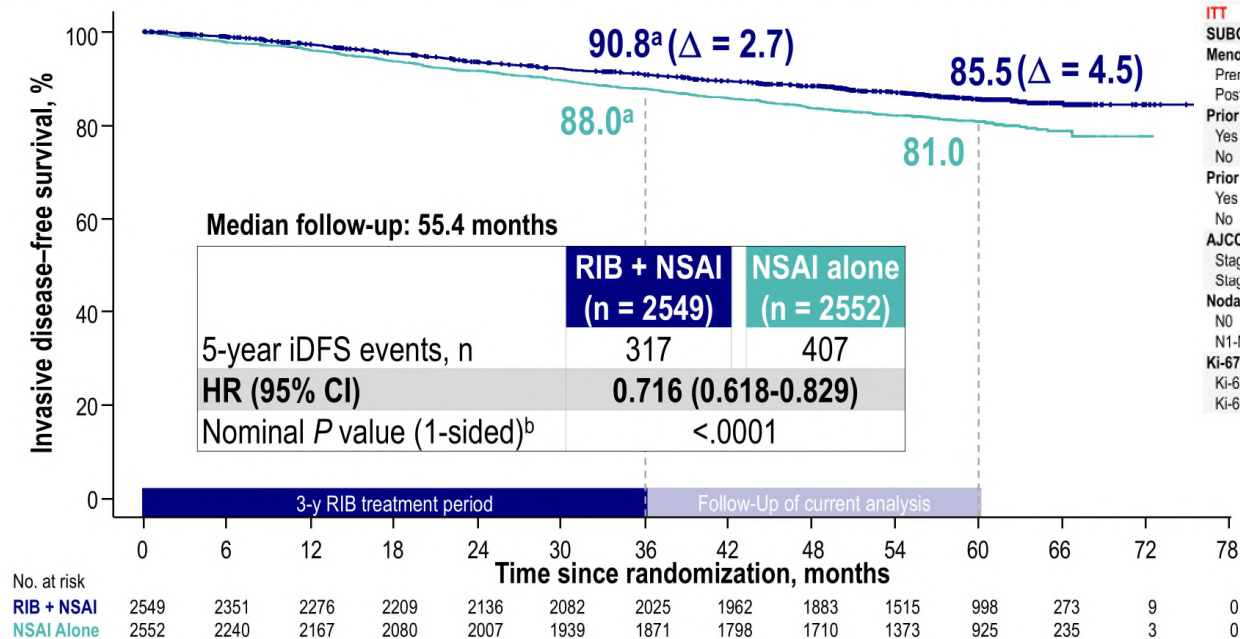
^a Enrollment of patients with stage II disease was capped at 40%. ^b Per investigator choice. ctDNA/RNA, circulating tumor DNA/RNA; DDFS, distant disease-free survival; DRFS, distant recurrence-free survival; EBC, early breast cancer; ET, endocrine therapy; HR, hazard ratio; iDFS, invasive disease-free survival; ITT, intention to treat; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcomes; RIB, ribociclib; RFS, recurrence-free survival; STEEP, Standardized Definitions for Efficacy End Points. 1. ClinicalTrials.gov. Accessed November 8, 2023. <https://clinicaltrials.gov/study/NCT03701334>. 2. Slamon D et al. *Ther Adv Med Oncol*. 2023;15:1-16.

John Crown, M.D.

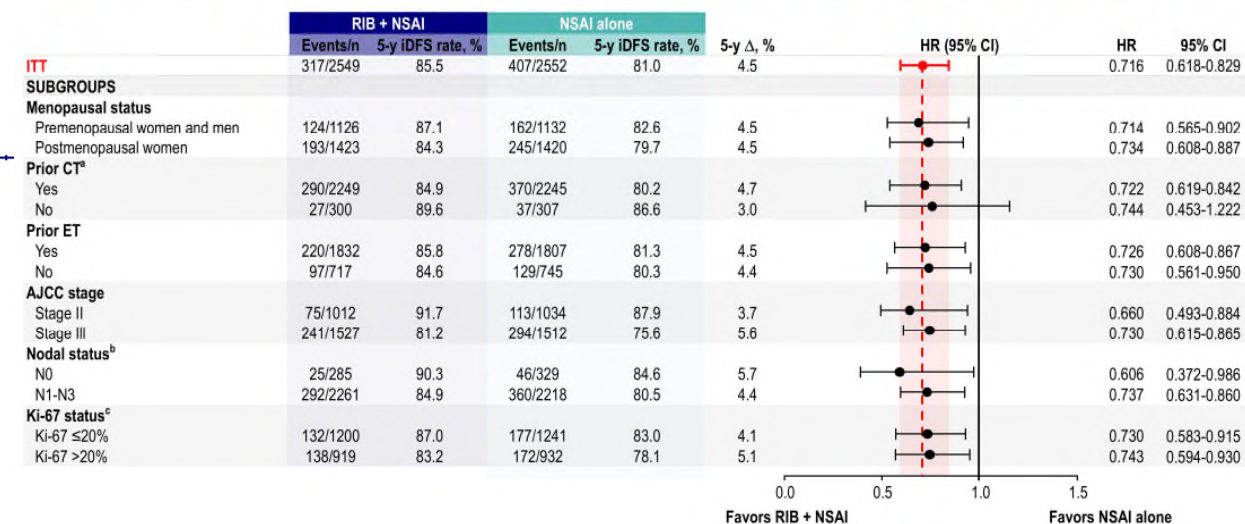
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iDFS in the ITT Population

With 55.4 months of follow-up, RIB continues to demonstrate a durable iDFS benefit

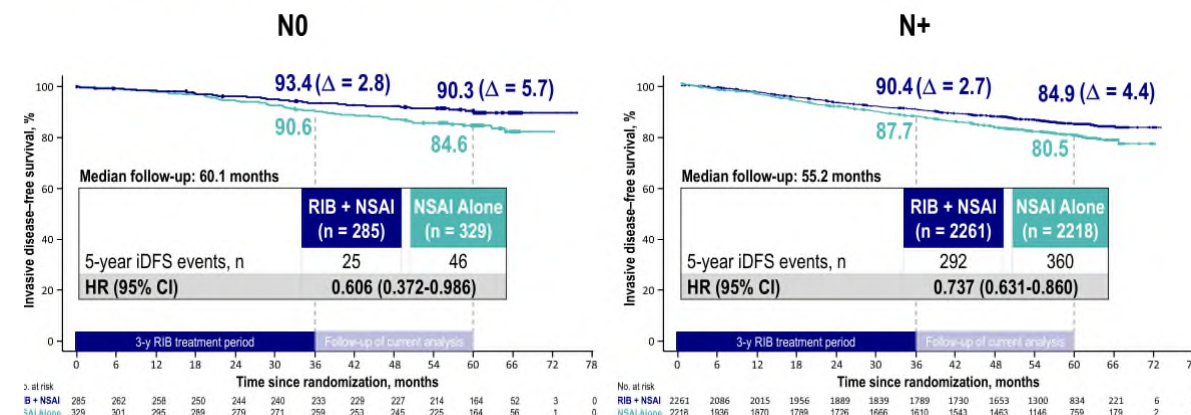


Consistent iDFS Outcomes Across Key Prespecified Subgroups



iDFS by Nodal Status

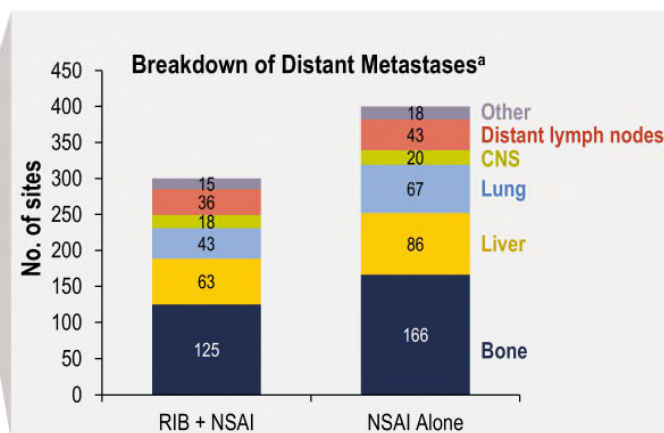
With a median of 2 years off RIB treatment, *RIB continues to demonstrate persistent benefit in patients with high-risk N0 disease and N+ disease*



RIB + NSAI Reduces Distant Disease

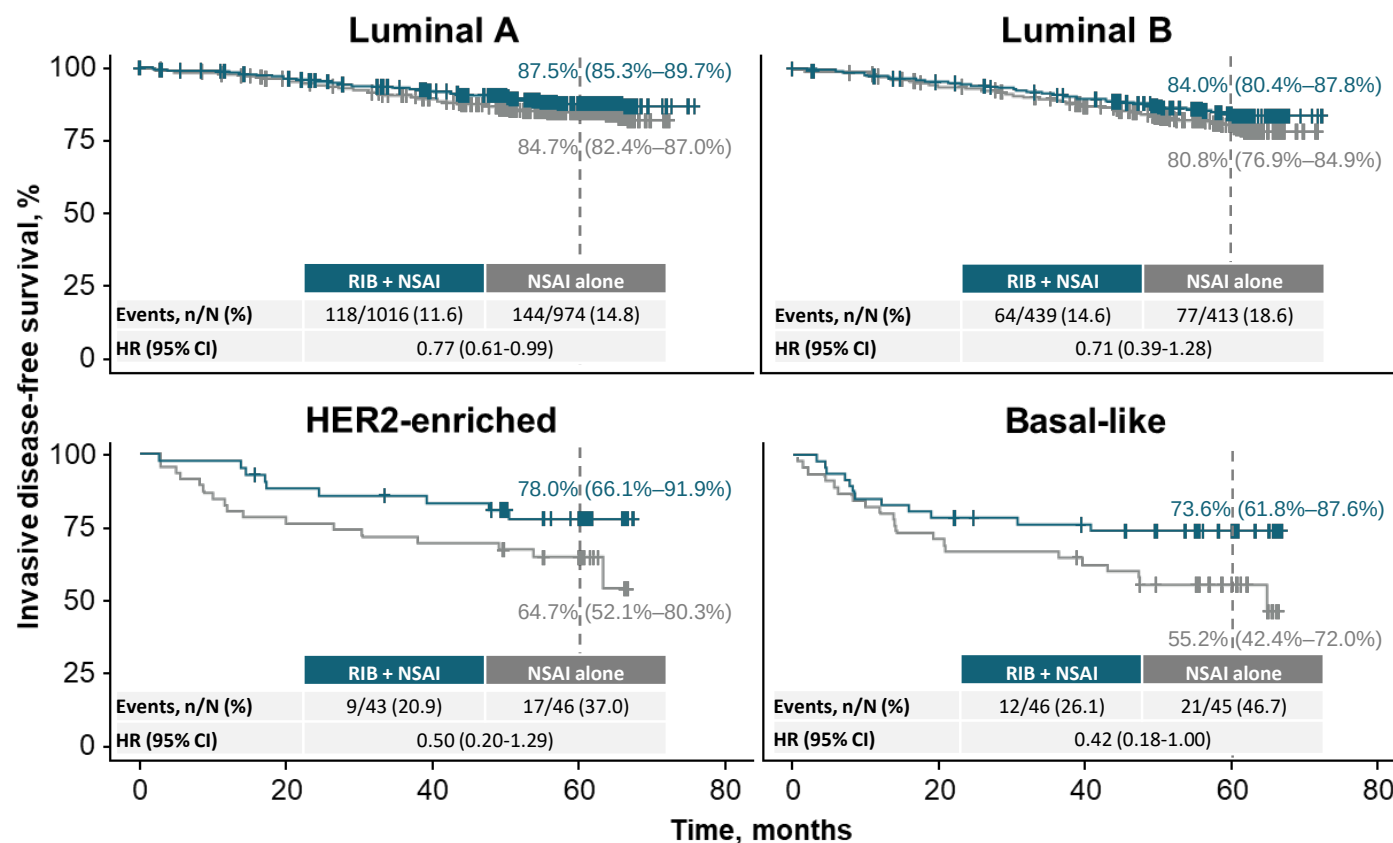
Most iDFS events were distant recurrences, which were more common in the NSAI-alone arm

ITT Population		
iDFS event type, n (%)		
	RIB + NSAI n = 2549	NSAI Alone n = 2552
Distant recurrence	207 (8.1)	290 (11.4)
Local/regional invasive recurrence	29 (1.1)	56 (2.2)
Second primary nonbreast cancer	49 (1.9)	52 (2.0)
Death	23 (0.9)	14 (0.5)
Invasive contralateral breast tumor	14 (0.5)	14 (0.5)
Invasive ipsilateral breast tumor	8 (0.3)	11 (0.4)

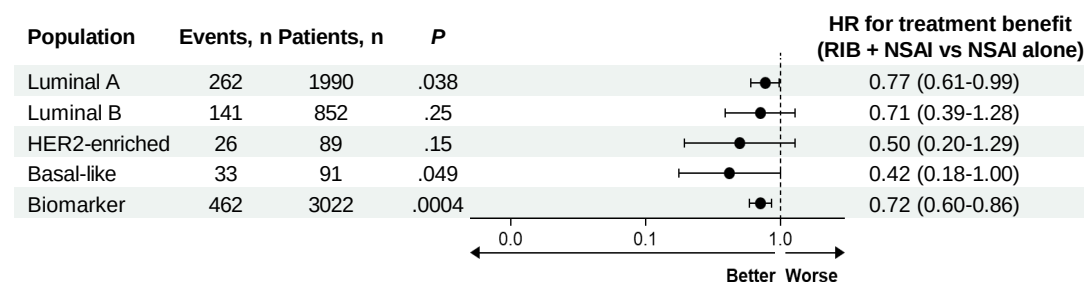


Ribociclib treatment benefit was seen across all PAM50-based intrinsic subtypes

iDFS by Intrinsic Subtype^a



Ribociclib Treatment Benefit Across Intrinsic Subtypes^{a,b}



- Across treatment arms, PAM50 subtypes were strongly prognostic (hazard ratio vs luminal A: luminal B, 1.39; HER2-enriched, 2.62; basal-like, 3.92^c)
- No significant interaction between subtype and treatment was observed ($P=.34^d$)

HER2, human epidermal growth factor receptor 2; HR, hazard ratio; iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; PAM50, Prediction Analysis of Microarray 50; RIB, ribociclib.

^a HRs were estimated using Cox proportional hazards models stratified by the four main strata and including a term for biomarker-by-treatment interaction. ^b The p-values for treatment effects within individual biomarker subgroups are model-based nominal two-sided Wald p-values without multiplicity correction. ^c HRs were obtained from Cox proportional hazards models stratified by the four main strata and adjusted for treatment group. ^d Nominal two-sided p-value from likelihood ratio test without multiplicity correction.



lidERA Study Design

Adjuvant Giredestrant

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

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

N = 4170

R
1:1

At least 5-year treatment duration

Giredestrant (30 mg PO QD)

SOC ET

Tamoxifen/anastrozole/letrozole/exemestane

5-year follow-up

Long-term
follow-up

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

Bardia et al. SABCS 2025

Study Population:

Medium risk:

- pN0 (> 1 cm) with high-risk biology - Grade 3, Ki67 $\geq$ 20%, or high genomic score
- pN1 with low-risk biology - Grade 1/2 + Ki67 < 20% + tumor $\leq$ 5 cm (+ low genomic score if done)

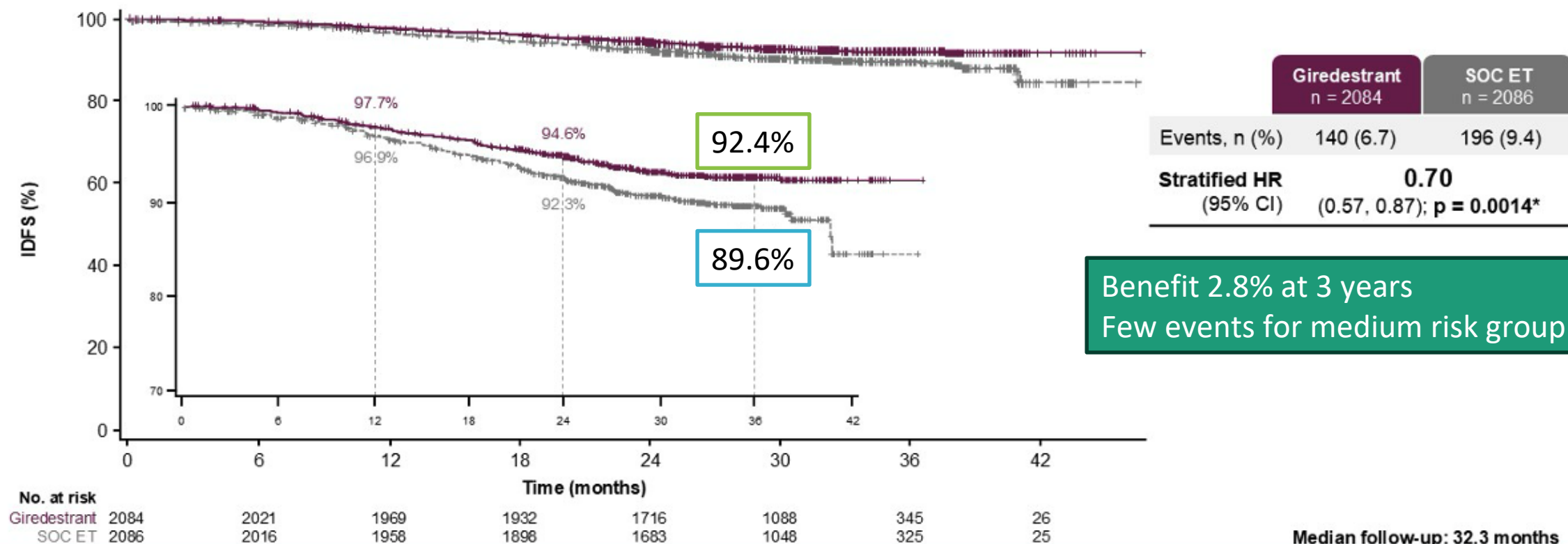
High risk:

- pT4, pN2, or pN3
- pN1 with high-risk biology - Grade 3, Ki67 $\geq$ 20%, tumor > 5 cm, or high genomic score

70% in this category

	Giredestrant n = 2084	SOC ET n = 2086
ER status, n (%)	n = 2075	n = 2083
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 (%)[†]	n = 2066	n = 2078
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[‡]	n = 2079	n = 2085
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)
Prior chemotherapy, n (%)		
No	396 (19.0)	450 (21.6)
Yes	1688 (81.0)	1636 (78.4)
Menopausal status, n (%)		
Pre-menopausal	849 (41.0)	838 (40.4)
Post-menopausal	1220 (59.0)	1236 (59.6)

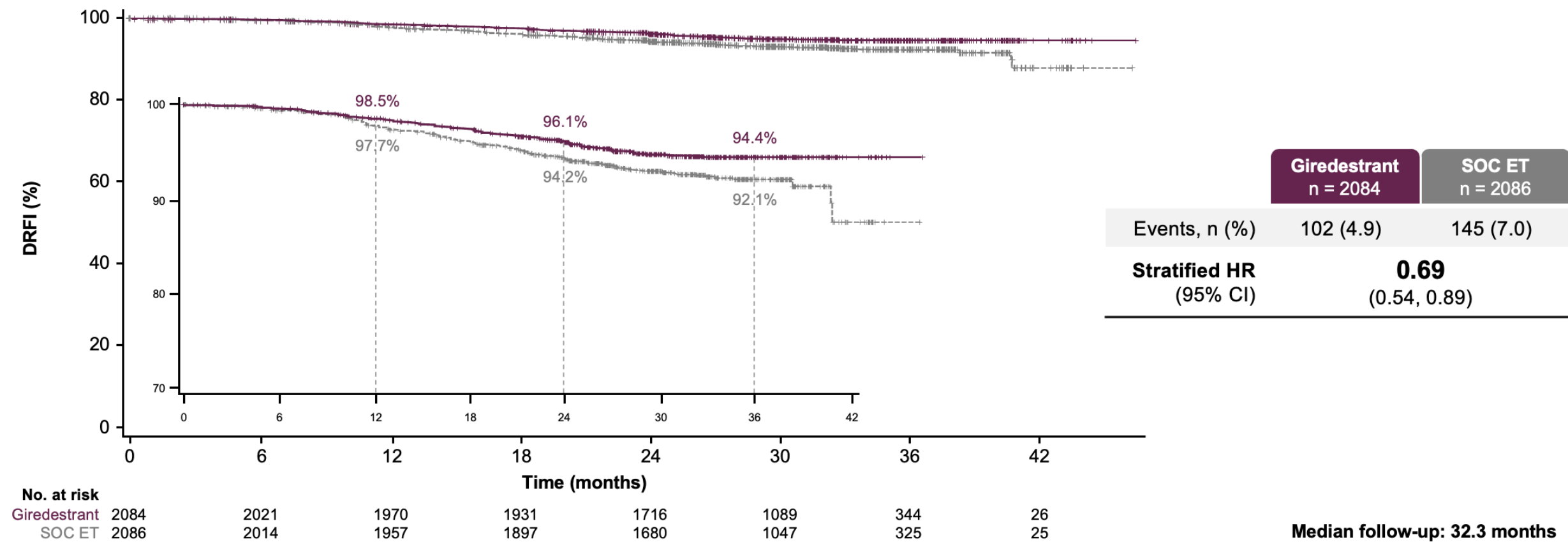
lidERA iDFS



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

Bardia et al. SABCS 2025

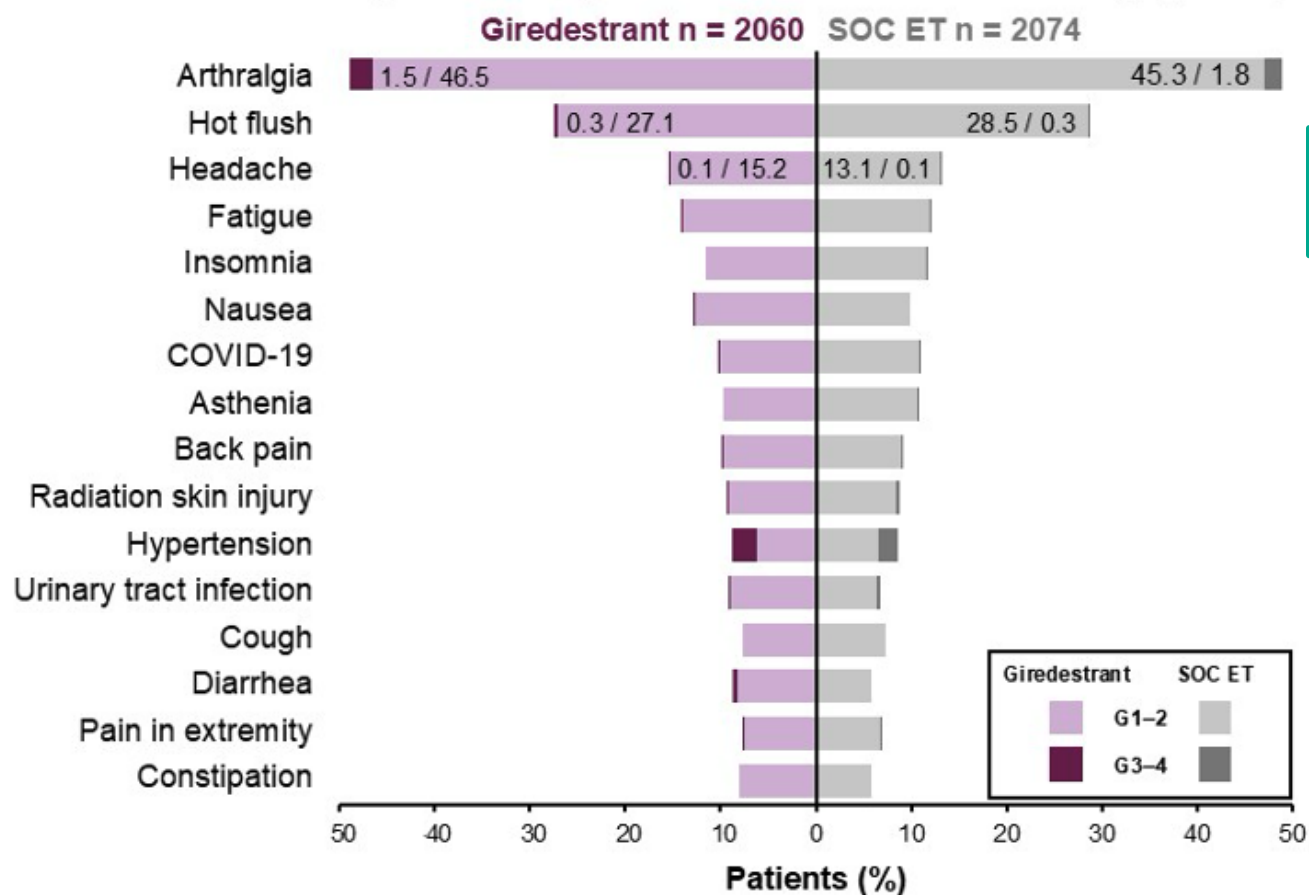
lidERA DRFI



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

Safety Profile: less arthralgia?

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



Selected AEs

	Giredestrant n = 2060	SOC ET n = 2074
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Patients, n (%) with treatment discontinuations due to AEs

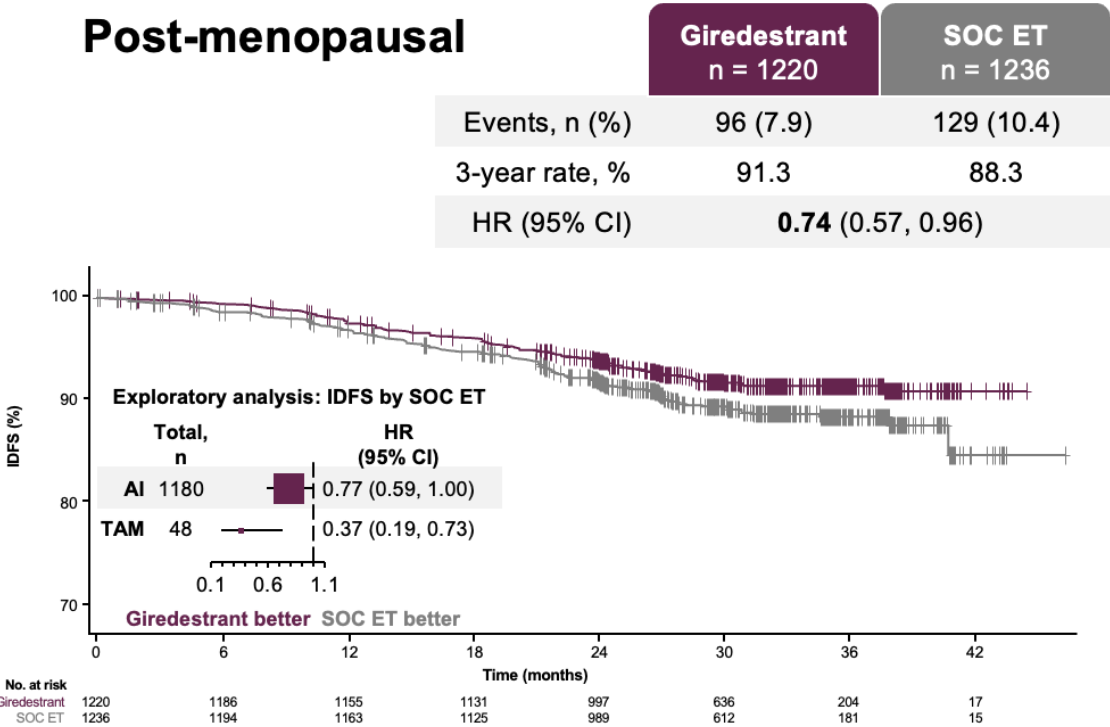
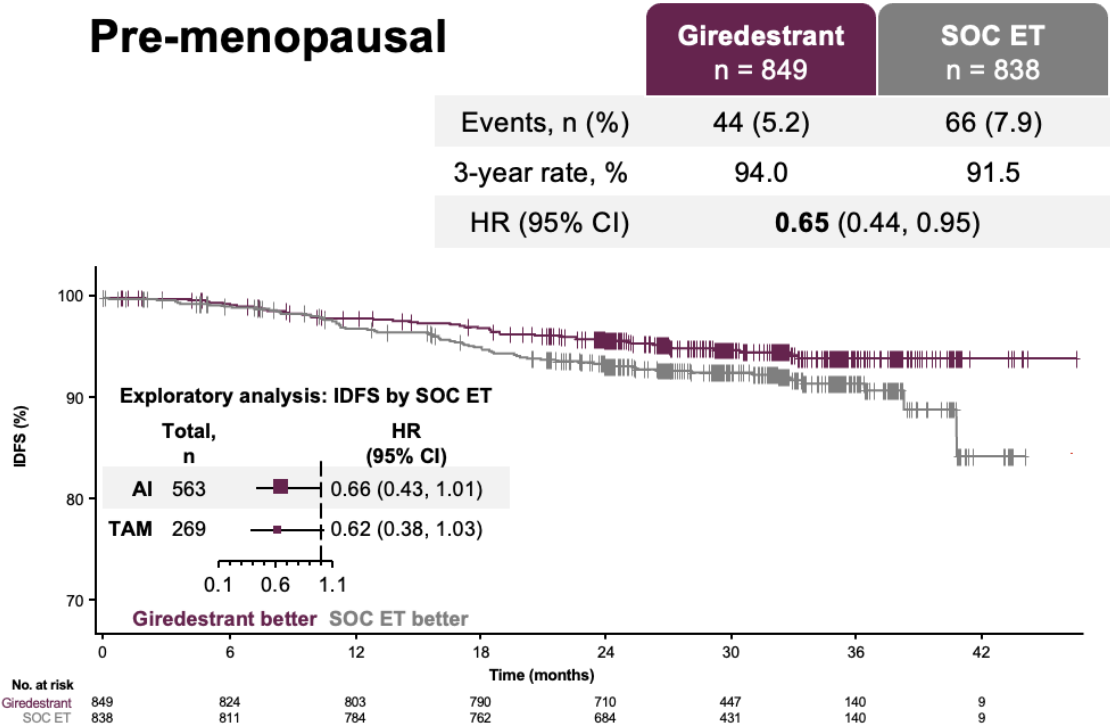
Musculoskeletal disorders	38 (1.8)	92 (4.4)
• Arthralgias (PT)	32 (1.6)	76 (3.7)
Vasomotor disorders	2 (< 0.1)	18 (0.9)
• Hot flush (PT)	1 (< 0.1)	16 (0.8)

	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)

IDFS by Menopausal status

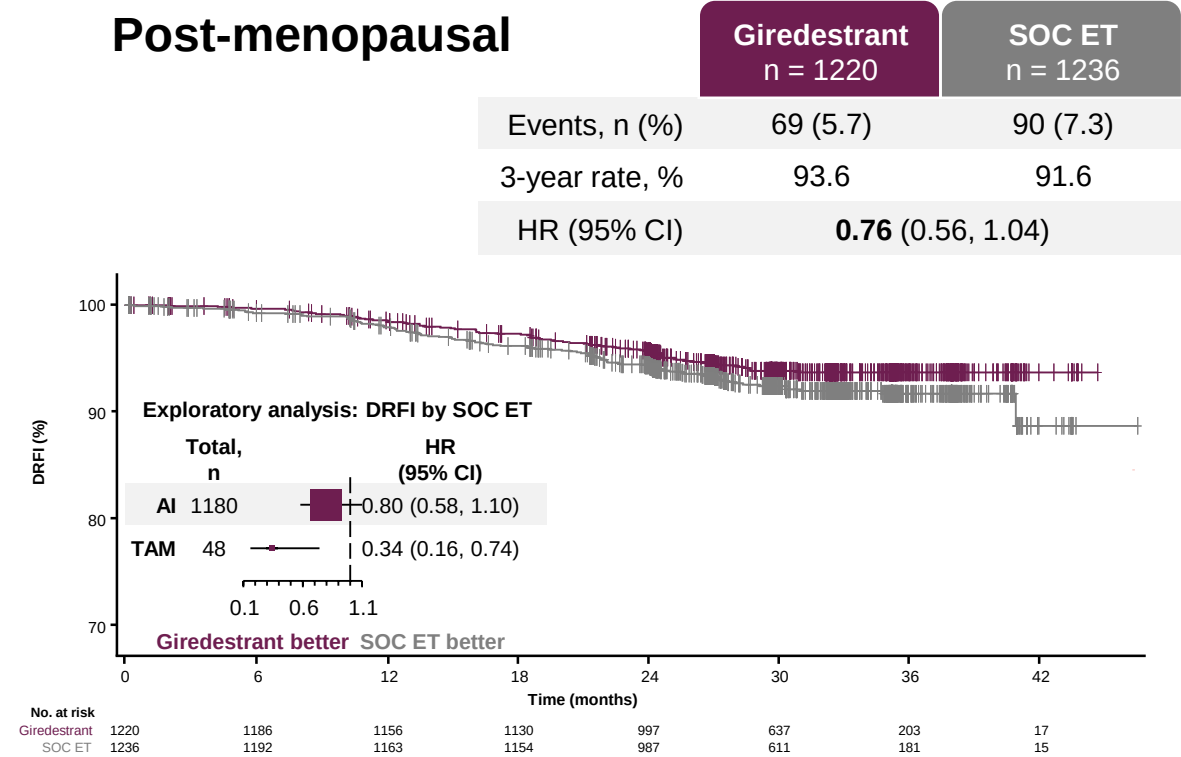
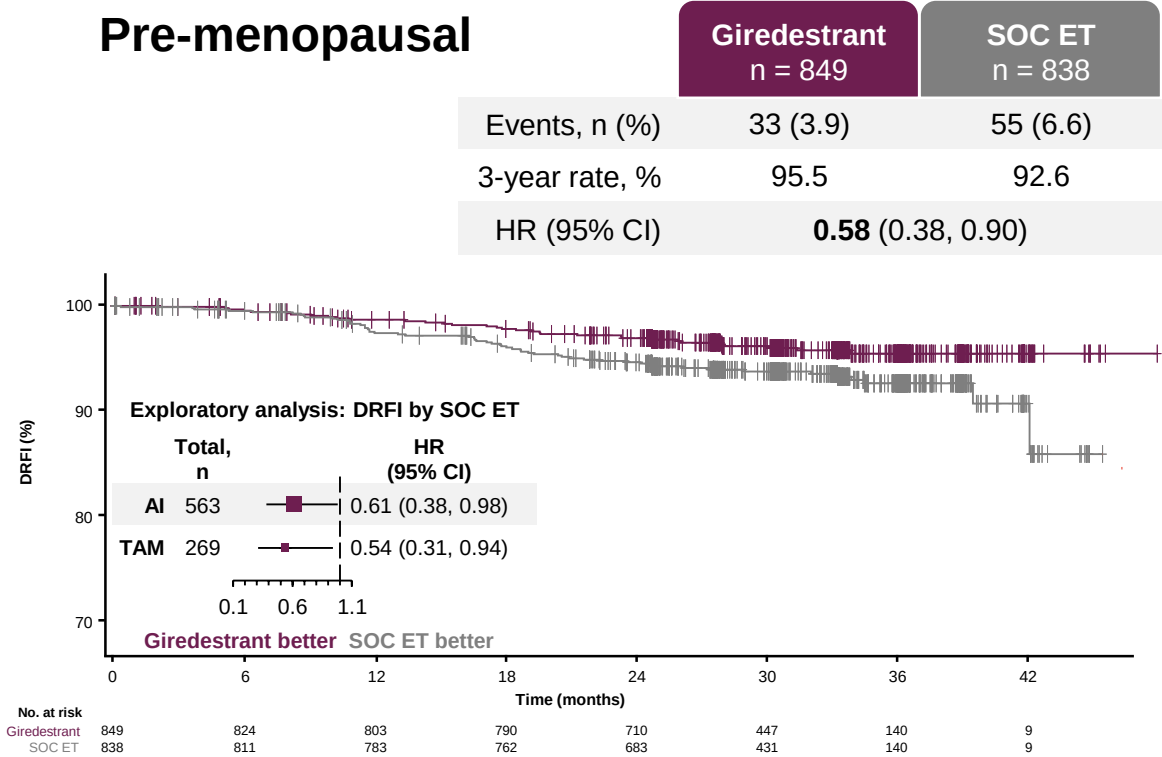


Giredestrant showed IDFS benefit and higher 3-year rates in both pre-menopausal and post-menopausal subgroups

Data cutoff: August 8, 2025. HR estimates are unstratified vs SOC ET.
AI, aromatase inhibitor; CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; IDFS, invasive disease-free survival; SOC, standard-of-care; TAM, tamoxifen.



DRFI by menopausal status



Giredestrant showed DRFI benefit and higher 3-year rates in both pre-menopausal and post-menopausal subgroups

Data cutoff: August 8, 2025. HR estimates are unstratified vs SOC ET.
AI, aromatase inhibitor; CI, confidence interval; DRFI, distant recurrence-free interval; ET, endocrine therapy; HR, hazard ratio; SOC, standard-of-care; TAM, tamoxifen.





Carey SABCS 2025



Takeaways for the Clinic

- From OPTIMA, we now have growing data on molecular risk assessment with the Prosigna test in high risk clinical subtypes
 - o Short follow up, caution in 4-9 LN
 - o Premenopausal 1-3 LN, age >40, must get OFS
- Adjuvant CDK4/6 inhibitors have demonstrated significant improvements in IDFS for high risk HR+HER- EBC
 - o OS benefit demonstrated with adjuvant **abemaciclib** (higher risk population)
 - o iDFS benefit with adjuvant **ribociclib** even in node negative with high risk features
- Adjuvant **giridestrant** improves IDFS at early follow up (2.75 y)
 - o 3-year IDFS 92.4% vs 89.6%
- If approved, could we use giridestrant:
 - o after completion of CDK4/6i?
 - o instead of AI for patients who cannot tolerate CDK4/6i or their AI
- Await data on switching to SERD after CDK4/6i + AI and/or combination CDK4/6i + oral SERD

Advanced Stage HR+ Disease

Monotherapy oral SERDs, PROTAC:

EMERALD, EMBER-3, VERITAC-2

Combinations:

Oral SERD + CDK4/6i: EMBER-3, ELEVATE

Oral SERD + everolimus: evERA, ELEVATE

Fulvestrant combinations: VIKTORIA-1

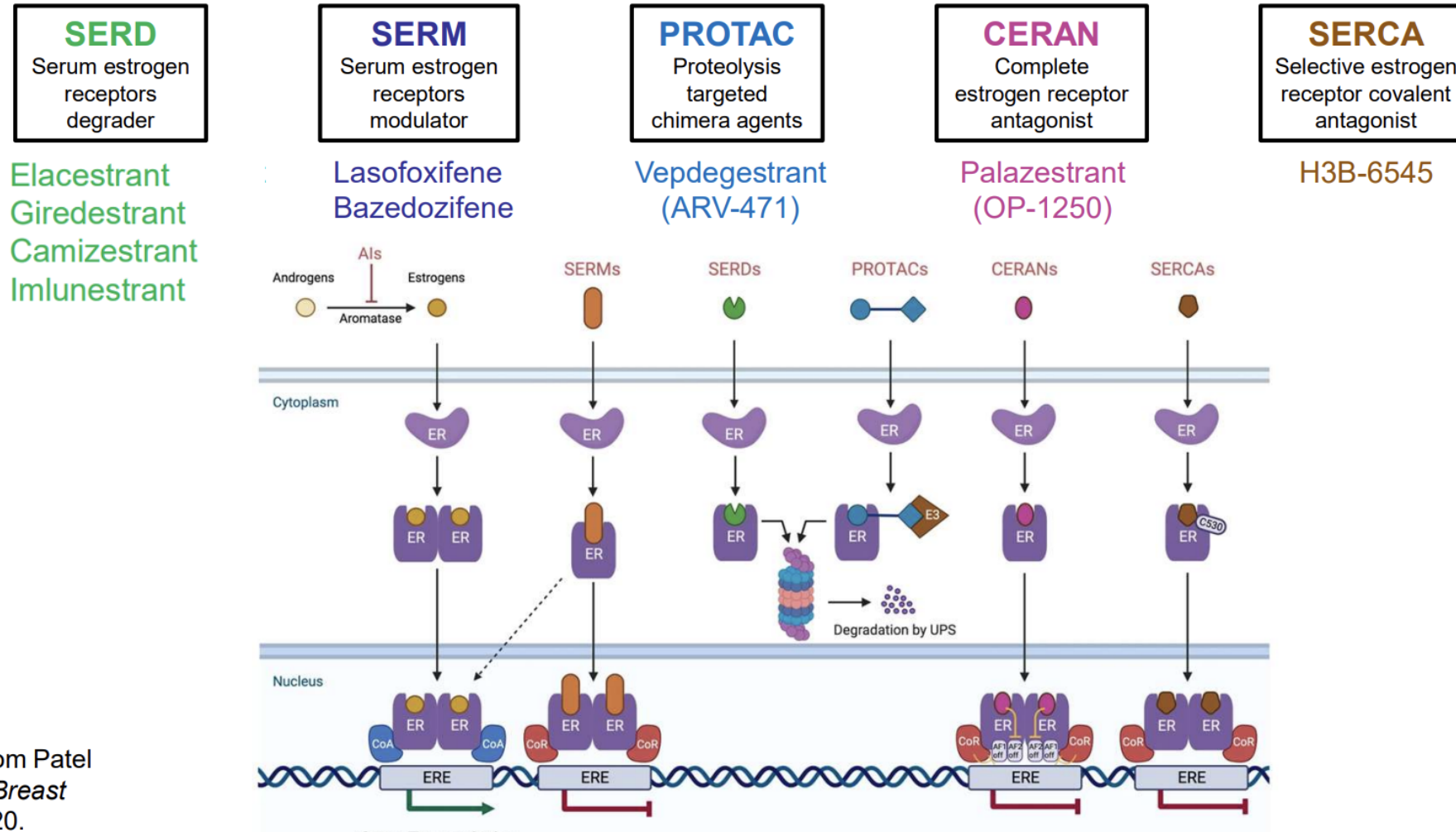
Switch strategies: SERENA-6



Treatment Landscape for HR+/HER2- mBC (2025)

First Line	Second Line	Later Line +
ET + CDK4/6i	<i>PIK3CA</i>_{mut} Fulvestrant + Alpelisib <i>PIK3CA</i>_{mut} Fulvestrant + Capivasertib <i>AKT1/PTEN</i>_{alt} Fulvestrant + Capivasertib <i>ESR1</i>_{mut} Elacestrant; Imlunestrant  <i>gBRCA</i>_{mut} Olaparib; Talazoparib	T-DXd (HER2-low or ultralow) Sacituzumab Govitecan Dato-DXd  Chemotherapy
ET + CDK4/6i + Inavolisib (High risk, <i>PIK3CA</i> _{mut})		
	No targetable mutation Switch CDK4/6i + ET Everolimus + ET Chemotherapy T-DXd (HER2-low or ultralow)	

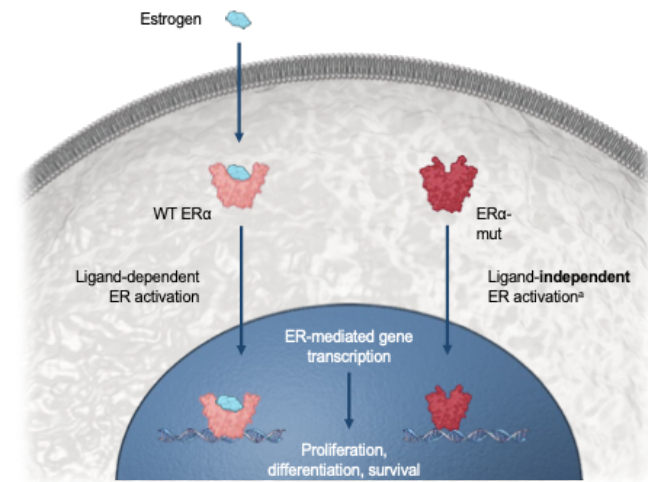
Background: Alphabet soup of novel ER targeting agents



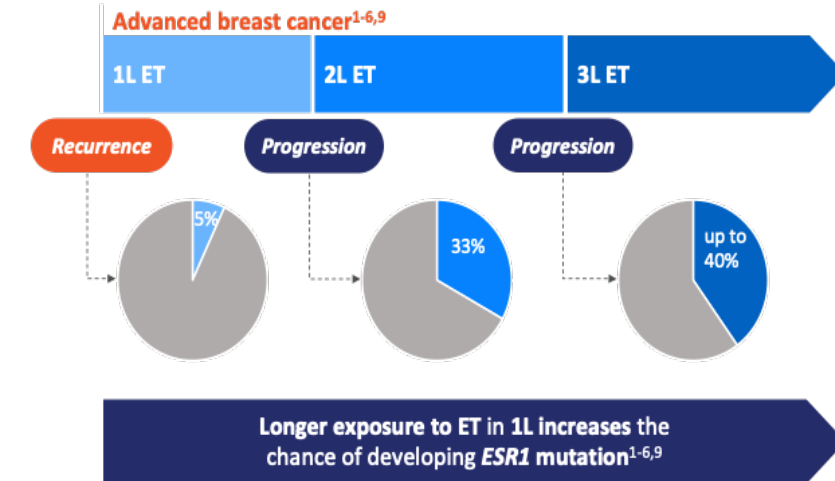
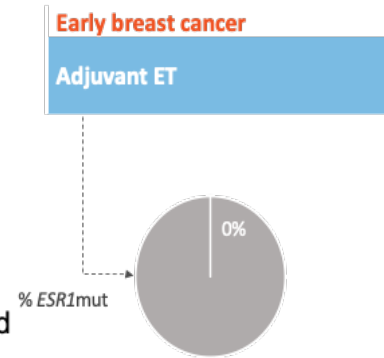
Adapted from Patel
et al. *NPJ Breast*
2023;9(1):20.

ESR1 Mutations Lead to Ligand Independent ER Activation and Constitutive ER Signaling, Driving Tumor Growth and are Key Drivers of Resistance

Mechanisms of Resistance to Endocrine Therapy Most ESR1 Mutations Arise After Progression on 1L mBC Therapy

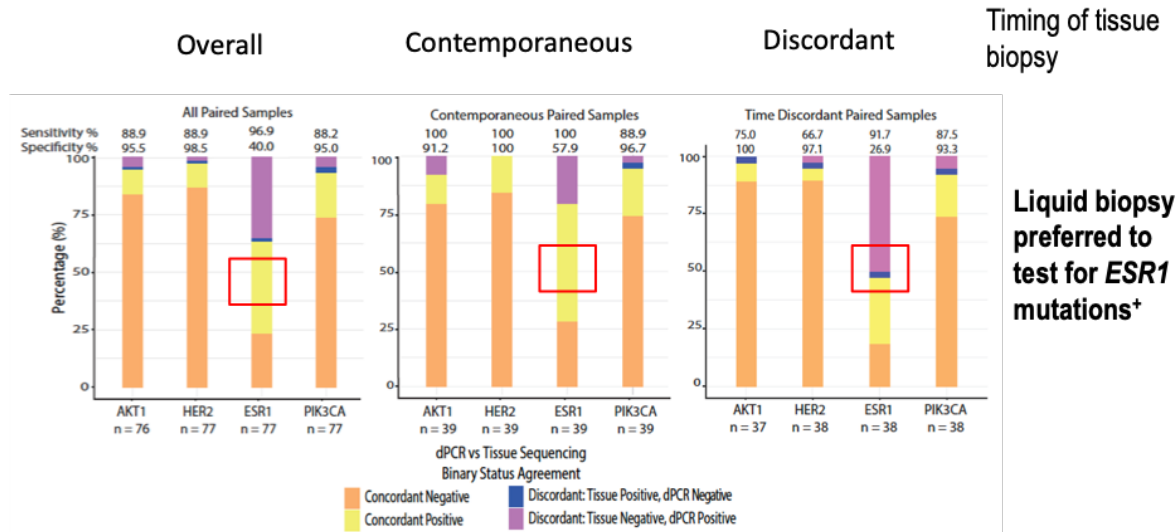


- *ESR1* mutations result in constitutive ER signaling and altered ERα function, leading to increased proliferation, differentiation and survival
- *ESR1* mutations have been associated with endocrine resistance, visceral metastases and poorer outcomes
- *ESR1* mutations predominantly occur after ET in the metastatic setting, leading to resistance to AIs or fulvestrant

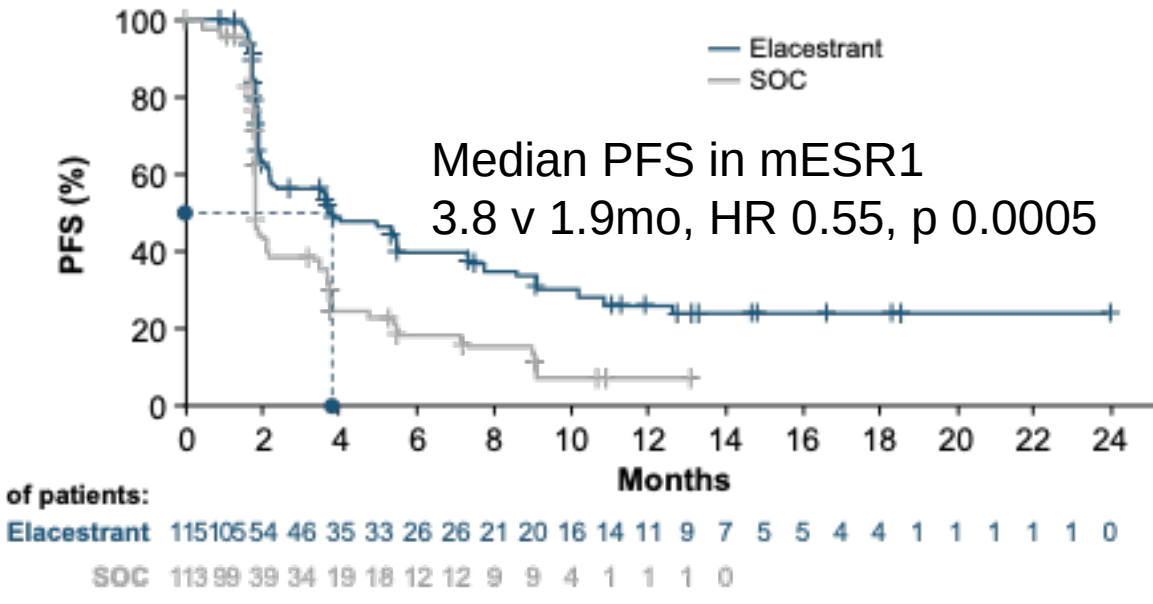
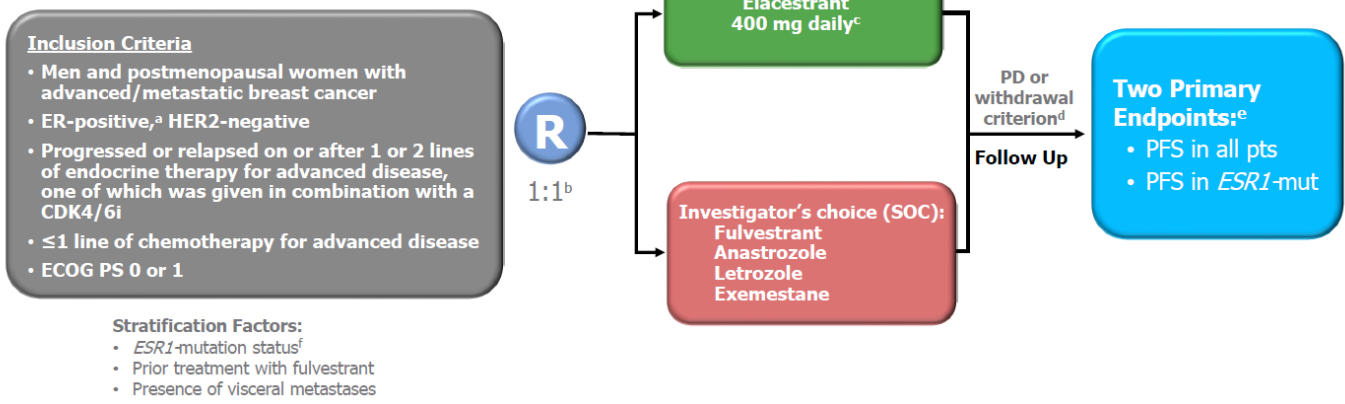


ctDNA vs paired tumor sequencing

Substantially more *ESR1* mutations identified in liquid biopsy



EMERALD: Randomized Phase III study all patients prior CDK4/6i



^aDocumentation of ER+ tumor with ≥ 1% staining by immunohistochemistry; ^bRecruitment from February 2019 to October 2020; ^cProtocol-defined dose reductions permitted; ^dRestaging CT scans every 8 weeks; ^eBlinded Independent Central Review; ^f*ESR1*-mutation

Every patient had prior ET + CDK4/6i¹

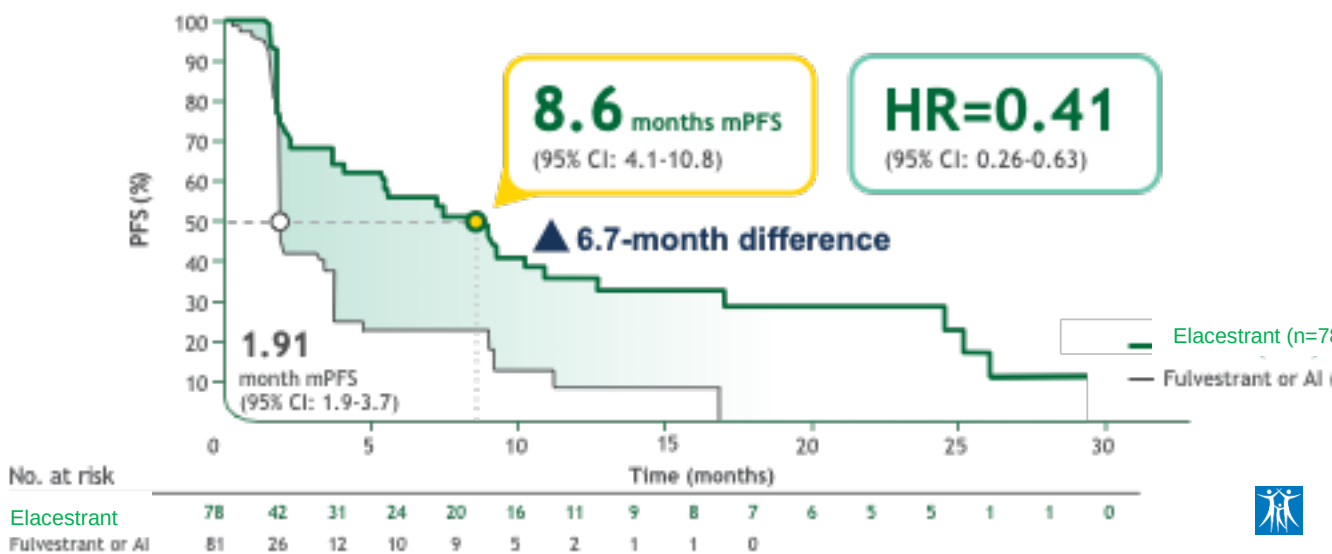
-24% of patients had primary endocrine resistance³

-25% of patients had prior chemotherapy* in the advanced or metastatic setting¹

-24% of patients had prior fulvestrant¹

72% had visceral metastases²

mPFS in patients with prior ET + CDK4/6i for ≥12 mos



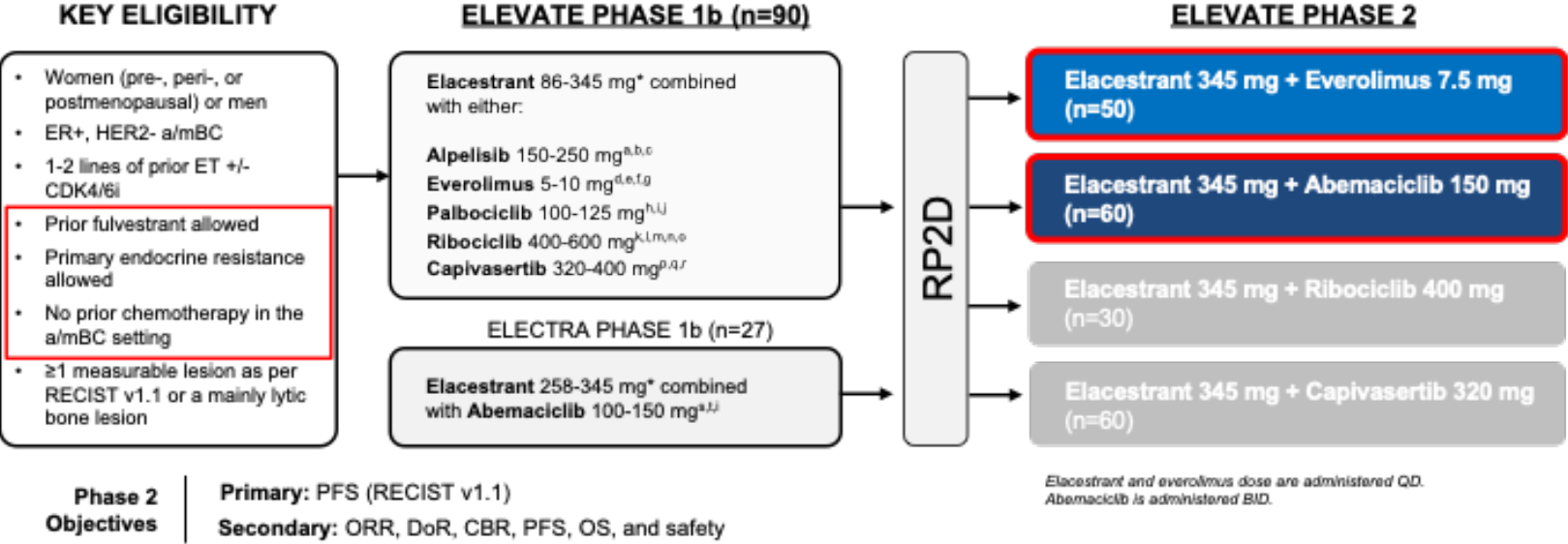
Real World Data in Pts with mESR1 MBC

mTTNT in two real world settings mirrored EMERALD trial results
Patients in the real world are being are benefitting!

	Rugo et al. Komodo Research Database (n=306)		Lloyd et al. GuardantINFORM (n=756)		Bardia et al. EMERALD subgroup analysis (n=78)	
Baseline characteristics	n	%	n	%	n	%
Prior ET +/- CDK4/6i for mBC	275	90%	642	83%	78	100%
Prior ET +/- CDK4/6i ≥12 mo	287	94%	-	-	78	100%
Prior chemo in mBC	153	50%	312	41%	16	21%
Prior fulvestrant in mBC	221	72%	402	53%	13	17%
No prior fulvestrant	85	28%	354	47%	65	83%
Co-existing ESR1 and PI3K pathway mutations	130	43%	234	31%	27	35%
Effectiveness		mTTNT, mo		mTTNT, mo		mPFS, mo
2nd line and earlier	-	-	203	8.8	-	-
2nd-3rd line	128	8.2	-	-	78	8.6
Co-mutations	130	6.3	234	5.2	27	5.5



Elevate: Phase II Study of Elacestrant in Combination with Everolimus or Abemaciclib



Ela/Eve

- 72% visceral mets
- 20% primary endocrine resistance
- 100% prior CDK4/6i
- 50% ribociclib
- 70% one prior line of Rx
- 50% prior fulvestrant

Safety

Consistent with either everolimus + standard ET or elacestrant; no new safety signals observed

No bradycardia or photopsia

TEAE leading to elacestrant + everolimus drug withdrawal 6%

TEAE leading to elacestrant + everolimus drug dose reduction 2%

- Ela/Eve
 - **PFS 8.3 mo (4-10.2)**
 - 82.9% DCR
 - 19.5% ORR
 - 8.54 mo mDOR

Subgroup	Elacestrant + everolimus	
	N	mPFS, months (95% CI)
All patients	50	8.3 [4.0-10.2]
Visceral disease	36	7.7 [3.7-9.4]
No prior fulvestrant	25	8.3 [4.2-12.9]
No primary endocrine resistance	40	8.3 [4.0-12.9]
ESR1m	21	8.3 [3.5-12.9]
ESR1wt	27	9.0 [4.2-12.7]
PIK3CAm	25	8.3 [3.6-10.2]
PIK3CAwt	23	9.4 [4.0-NR]



Elevate: Elacestrant/Abemaciclib

Elacestrant/Abemaciclib

92% visceral mets
15% primary endocrine resistance
50% prior CDK4/6i
78% one prior line of Rx
30% prior fulvestrant

Safety

The safety profile is consistent with abemaciclib + standard ET or elacestrant; no new safety signals were observed
No bradycardia or photopsia
TEAE leading to elacestrant + abemaciclib drug withdrawal 0%
TEAE leading to elacestrant + abemaciclib drug reduction 5%

PFS: 14.3 months

91.2% DCR

24.6% ORR

14.75 mos mDOR

Elacestrant + abemaciclib			
Subgroup	N	mPFS, months (95% CI)	
All patients	60	14.3 [7.3-16.6]	
Visceral disease	55	14.3 [7.4-16.6]	
No prior fulvestrant	42	14.8 [8.7-NR]	
No primary endocrine resistance	51	14.3 [7.3-16.6]	

Follow Up Time, median (95% CI), months: Overall: 8.6 (6.5-12.6) - Arm C: 5.7 (4.6-8.7) - Arm D: 11.6 (8.5-13.4)

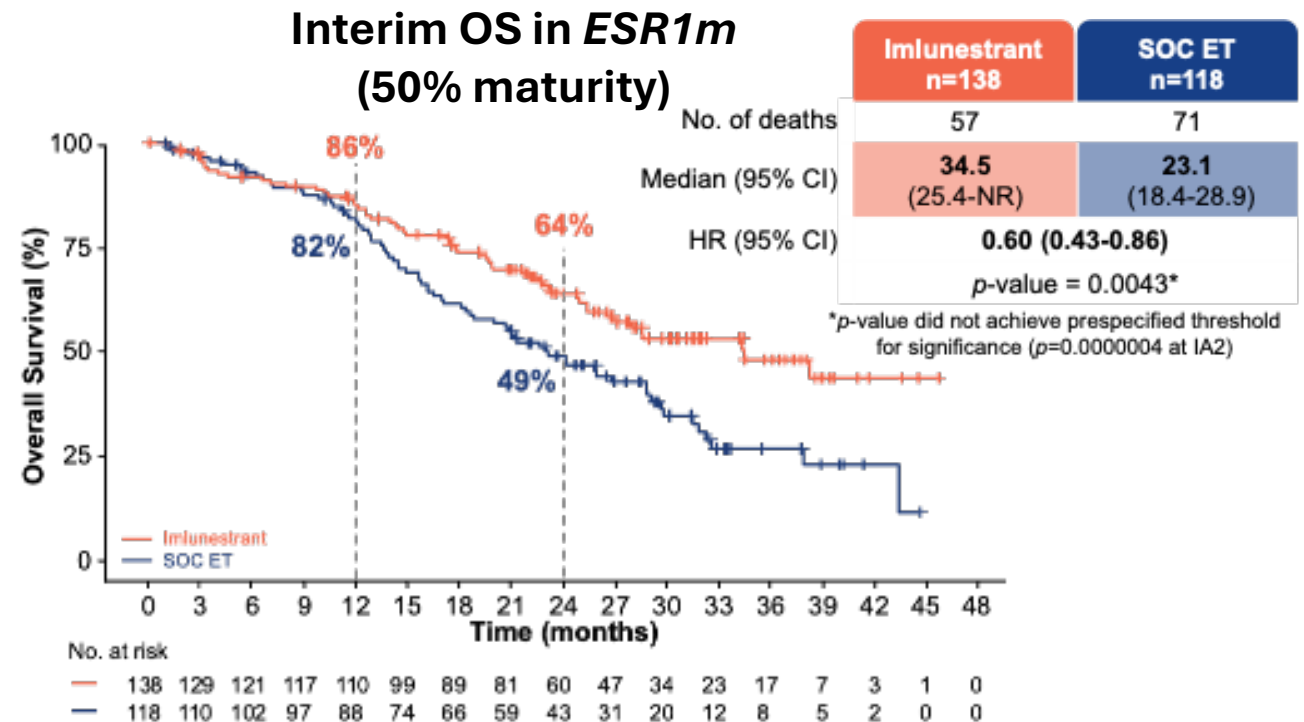
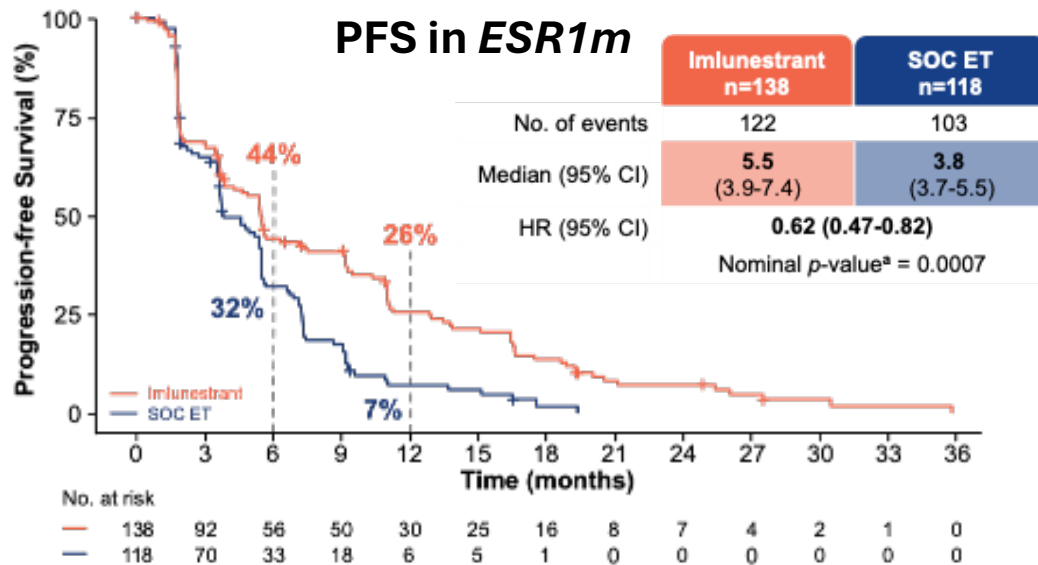
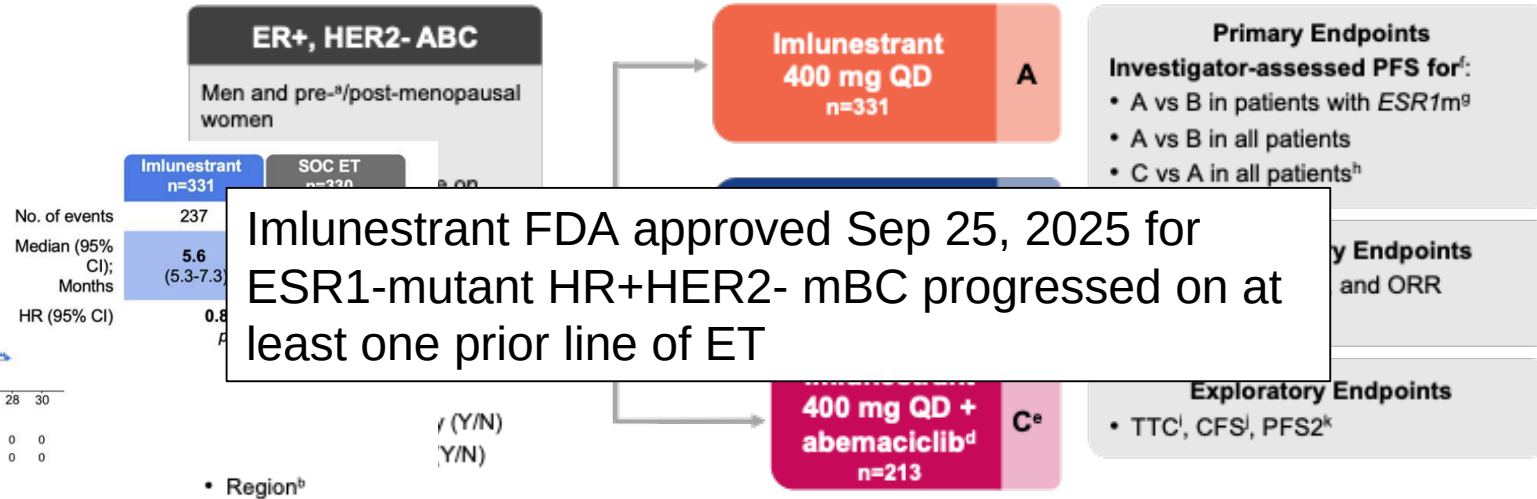
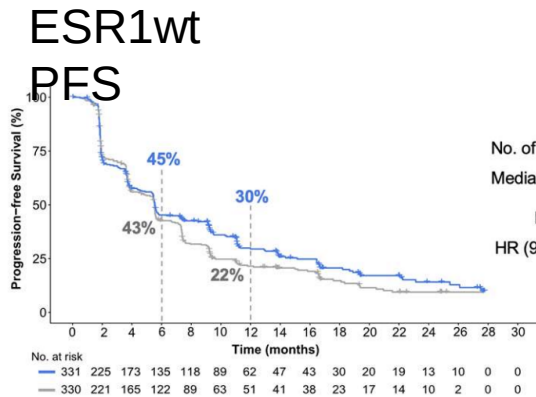
Maturity not reached for PFS (95% CI) for genomic subgroups (ESR1 / PIK3CA) or by prior CDK4/6i exposure

Arm C required prior CDK4/6i (palbociclib or ribociclib)

Arm D excluded prior CDK4/6i

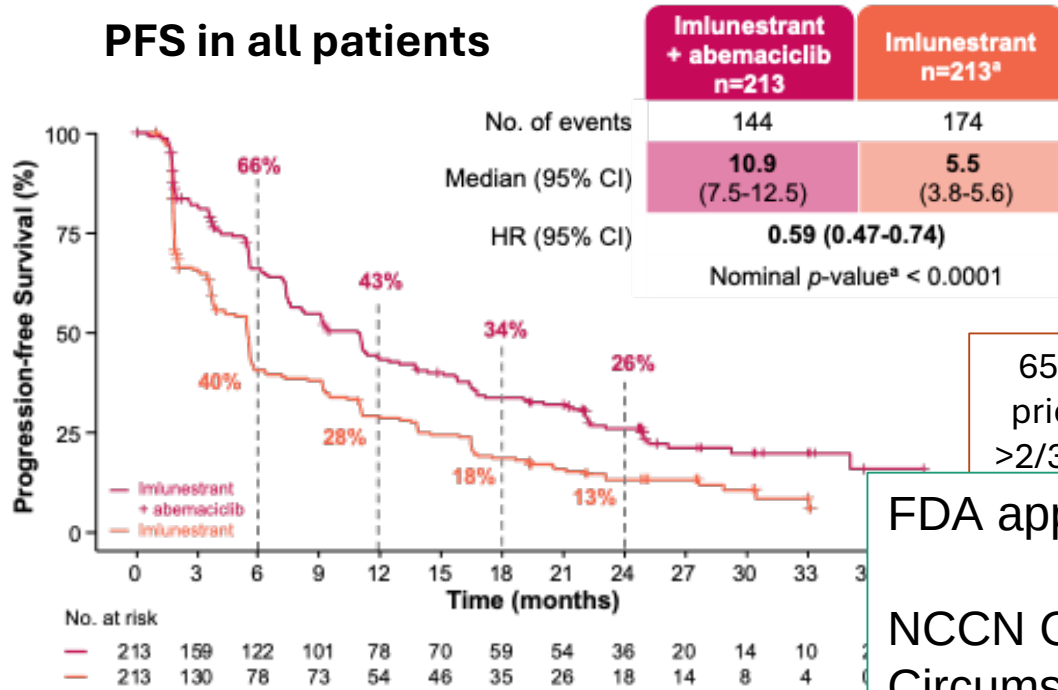


EMBER-3: Imlunestrant as 2nd Line Therapy for HR+ MBC



Imlunestrant/Abemaciclib vs Imlunestrant

PFS in all patients

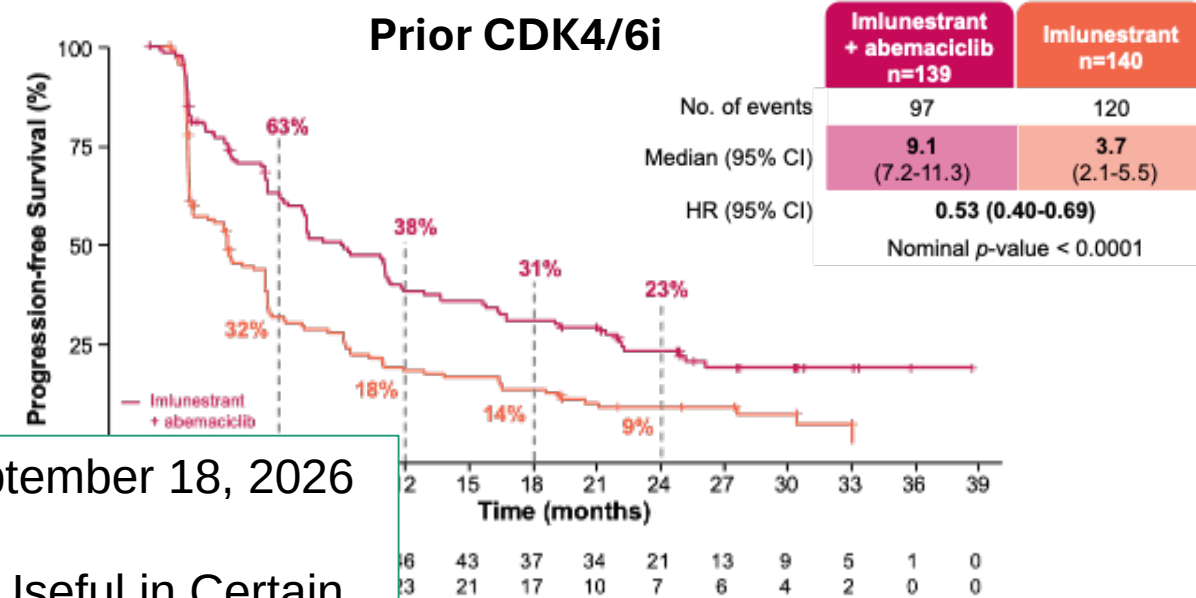


65 v 59% had
prior CDK4/6i;
>2/3 palbociclib

FDA approved September 18, 2026

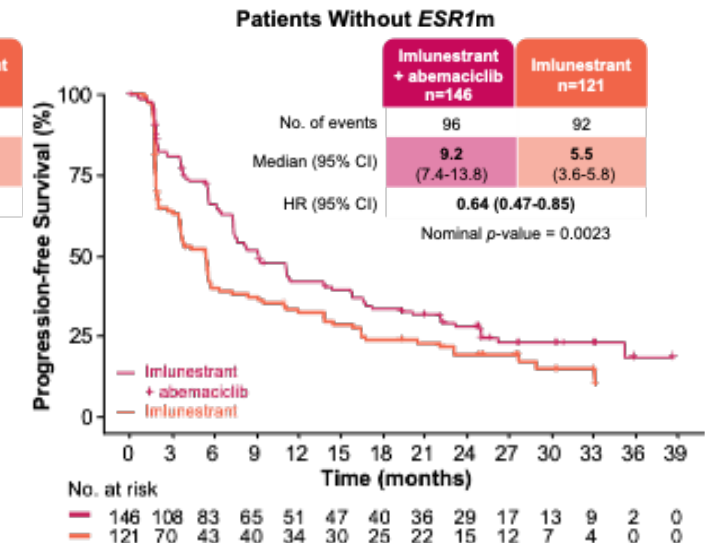
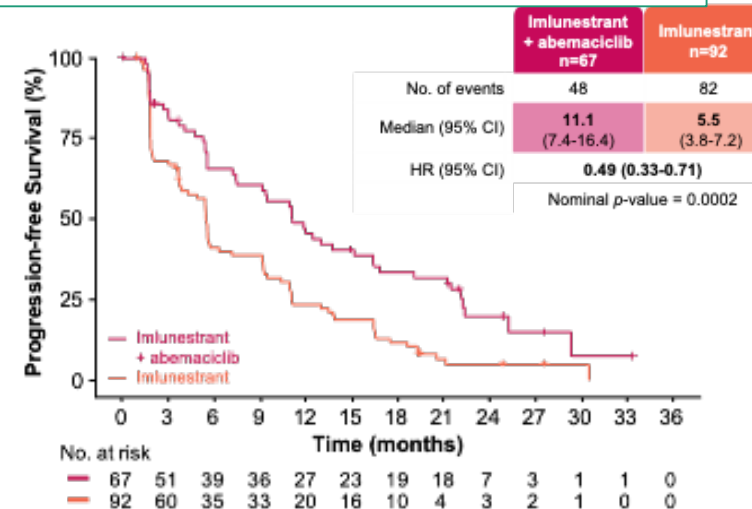
NCCN Guidelines Useful in Certain
Circumstances (2A)

Prior CDK4/6i



Benefit across PI3K pathway mutations

- Mutation
 - 7.6 v 3.8 mo (n=88 v 84, HR 0.57)
- No mutation
 - 11.3 v 5.6 mo (n=109 v 112, HR 0.59)
- Safety
 - As expected from each agent
 - 86% diarrhea
 - More dose reductions (39%), discontinuations in combination arm



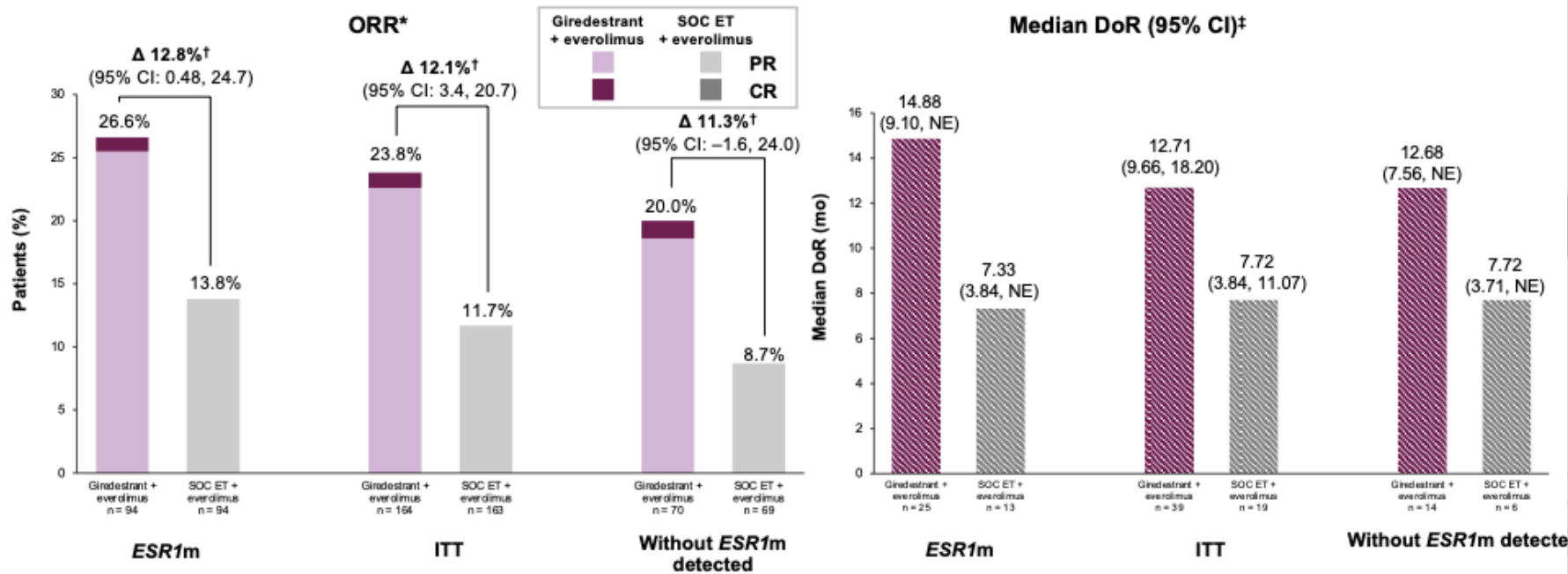
evERA: Phase III Trial of Giredestrant plus Everolimus in HR+ MBC Post CDK4/6i

Key eligibility

- ER+, HER2- aBC (1-3L)
- ≤ 2 prior lines of ET in the
- PD or relapse during/post
- No prior chemotherapy in
- Measurable disease per F bone metastases

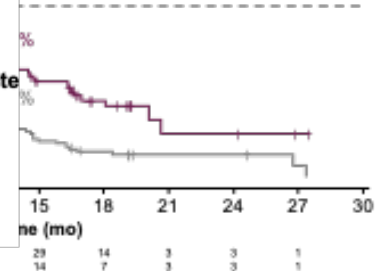
* Trial was enriched to 55% of patients (centrally tested via circulating tumor DNA)
† Patients had to receive ≥ 6 months of prior fulvestrant to be eligible for enrollment; prior fulvestrant

ORR and DoR in the ESR1m and ITT populations, and in patients without ESR1m detected



(1.1)
patients had an ESR1m

Giredestrant + everolimus n = 183	SOC ET + everolimus n = 190
126 (68.9)	163 (85.8)
8.77 (6.60, 9.59)	5.49 (4.01, 5.59)
0.56 (0.44, 0.71); p < 0.0001	



Data cutoff: 16 July 2025. Adapted from Mayer EL, et al. ESMO 2025 (oral LBA16) with permission. * Patients who had measurable disease at baseline; all responses were confirmed on two consecutive occasions ≥ 4 weeks apart. † Stratified analysis. ‡ Patients who had measurable disease at baseline and an objective response.

CI, confidence interval; CR, complete response; DoR, duration of response; ESR1m, ESR1 mutation; ITT, intention to treat; mo, months; NE, not evaluable; ORR, objective response rate; PR, partial response; SOC ET, standard of care endocrine therapy.

Presented by: Hope S. Rugo, MD.

Giredestrant + everolimus 102 65 41 52 28 13 6 2 2
SOC ET + everolimus 105 67 35 25 10 2 1 1 1

Giredestrant + everolimus 183 149 95 78 47
SOC ET + everolimus 190 131 66 58 27

Demographics

47% prior fulvestrant
25% CDK4/6i from
57% v 63%
and abemaciclib

Biomarkers

55% ESR1 n
35 vs 27% F
45 vs 42% p



Additional Data

In both the *ESR1m* and ITT populations, the magnitude of clinical benefit was consistent, regardless of

*PIK3CA*m and *PIK3CA*Δ
Duration of prior CDi
Choice of prior CDi
or abemaciclib)

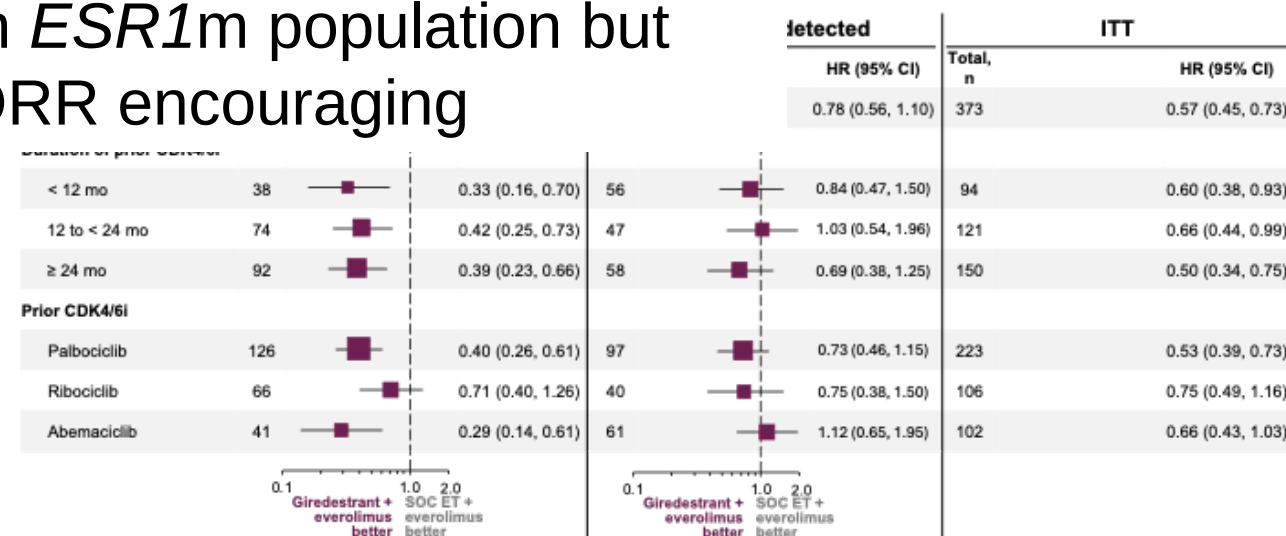
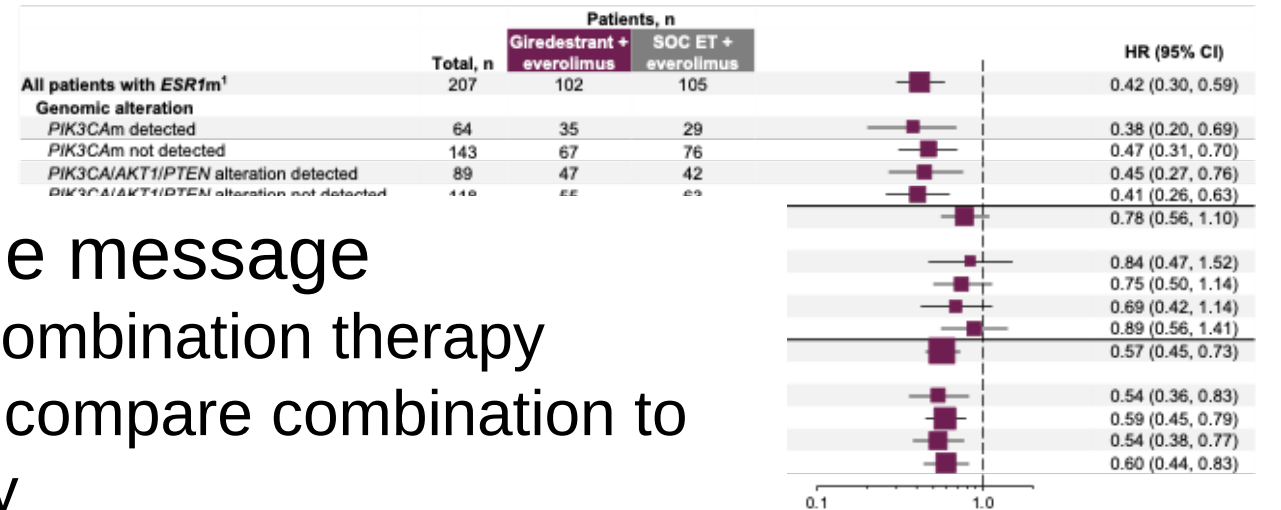
In secondary analysis, appeared restricted population

Safety as expected from individual agents

Giredestrant: 3.8% v 1% Gr1-2 bradycardia
No photopsia
Primary toxicity in both arms grade 1-2
stomatitis

Take home message

- Effective and safe combination therapy
- Only trial to directly compare combination to combination therapy
- Majority of impact in *ESR1m* population but benefit in ITT and ORR encouraging



VERITAC-2: PROTAC Phase III Trial

Trial Design

Key Eligibility Criteria

- Age ≥ 18 years old
- ER+/HER2- advanced or metastatic breast cancer
- Prior therapy:
 - 1 line of CDK4/6i + ET
 - ≤ 1 additional ET
 - Most recent ET for ≥ 6 months
 - No prior SERD (eg, fulvestrant, elacestrant)
 - No prior chemotherapy for advanced or metastatic disease
- Radiological progression during or after the last line of therapy

Randomization (1:1)

28-day Treatment Cycles

Vepdegestrant (n=313)
200 mg orally (once daily)

Fulvestrant (n=311)
500 mg IM
(days 1 and 15 of cycle 1; day 1 of subsequent cycles)

Stratification Factors:

- *ESR1* mutation^a (yes vs no)
- Visceral disease (yes vs no)

Primary Endpoint:

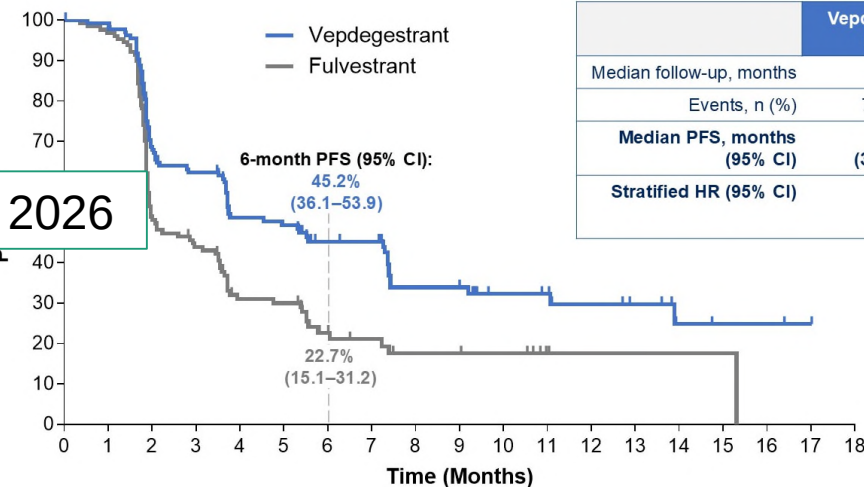
- PFS by BICR in – *ESR1m* population

FDA Approved May 1, 2026

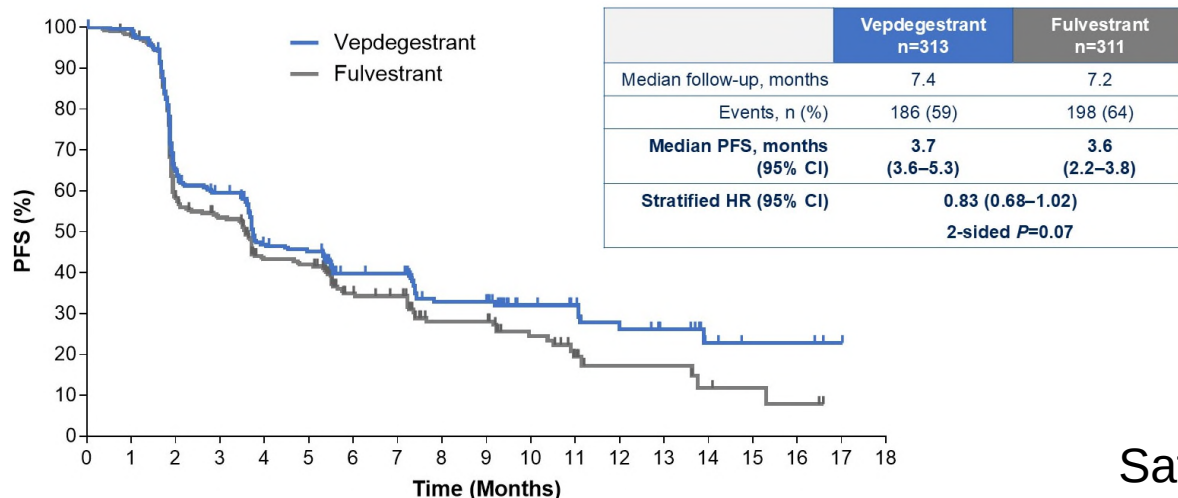
Secondary Endpoints:

- OS (key secondary)
- CBR and ORR by BIC
- AEs

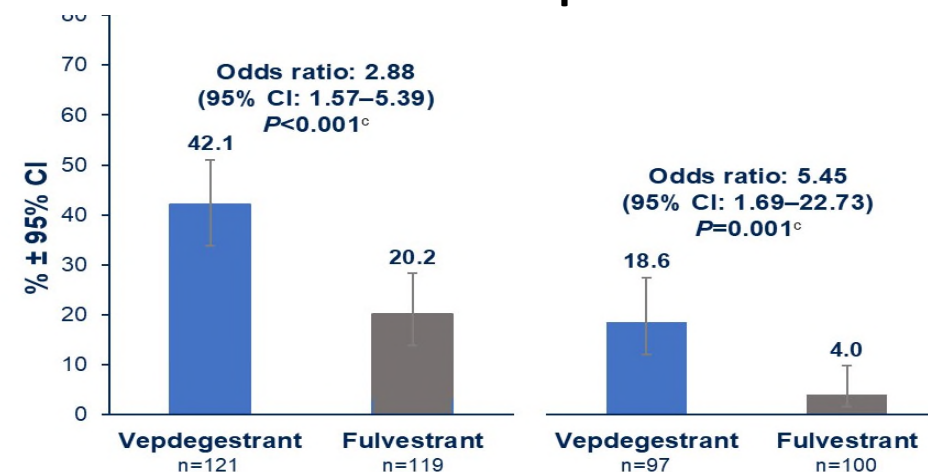
PFS by BICR in pts with *ESR1m*



PFS by BICR in All pts



CBR^a and ORR^b in pts with *ESR1m*

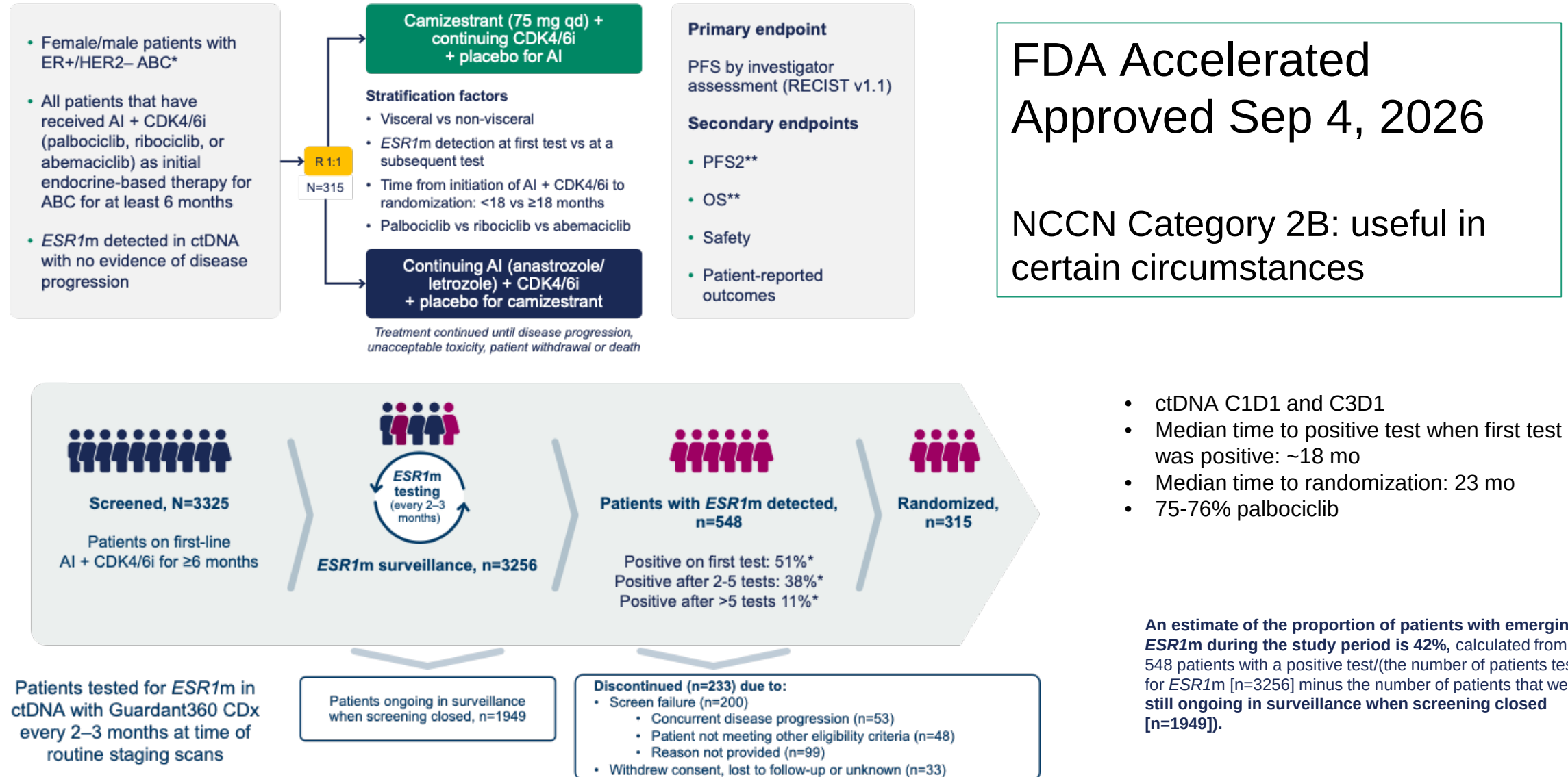


Safety: Well tolerated, mild increase in liver enzymes, minimal QT prolongation (11.1 ms)



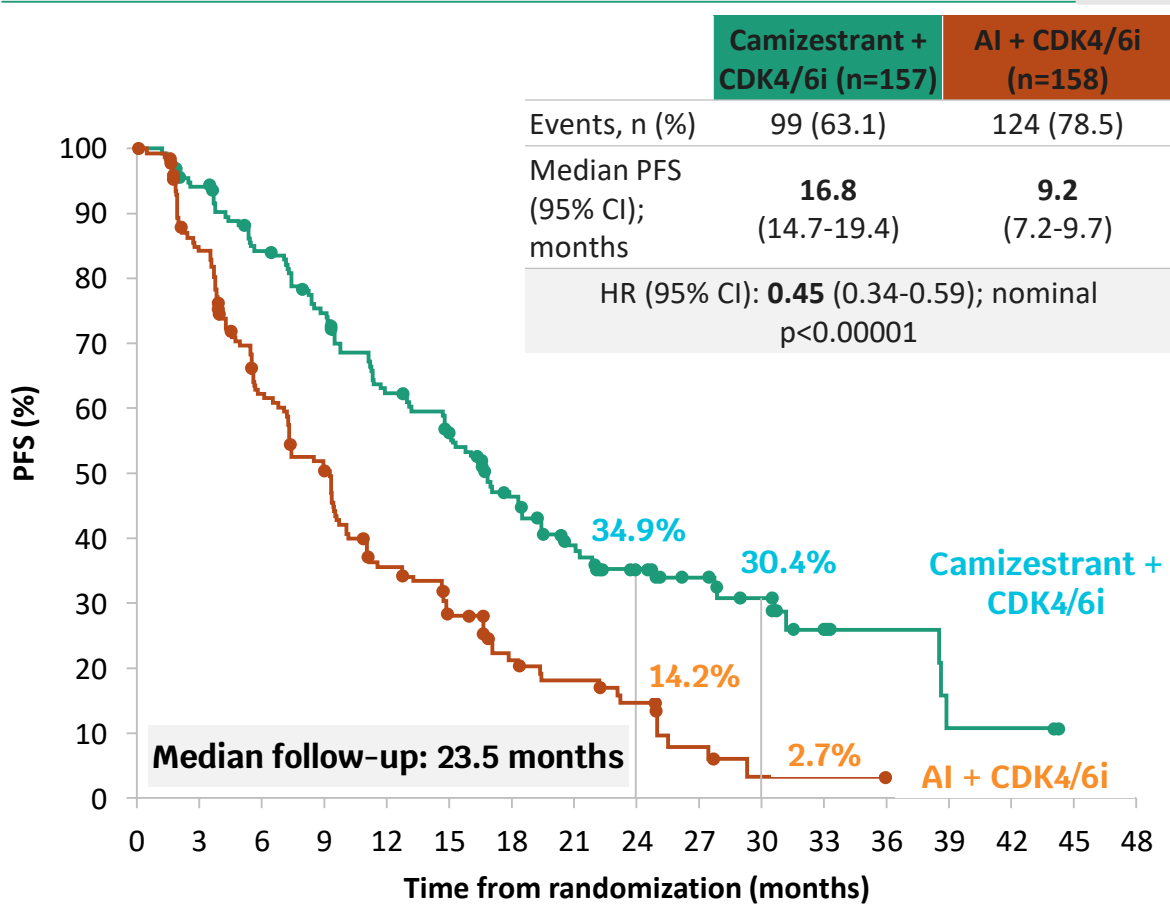
SERENA-6 Study Design and Disposition Over Time

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



SERENA6: Efficacy

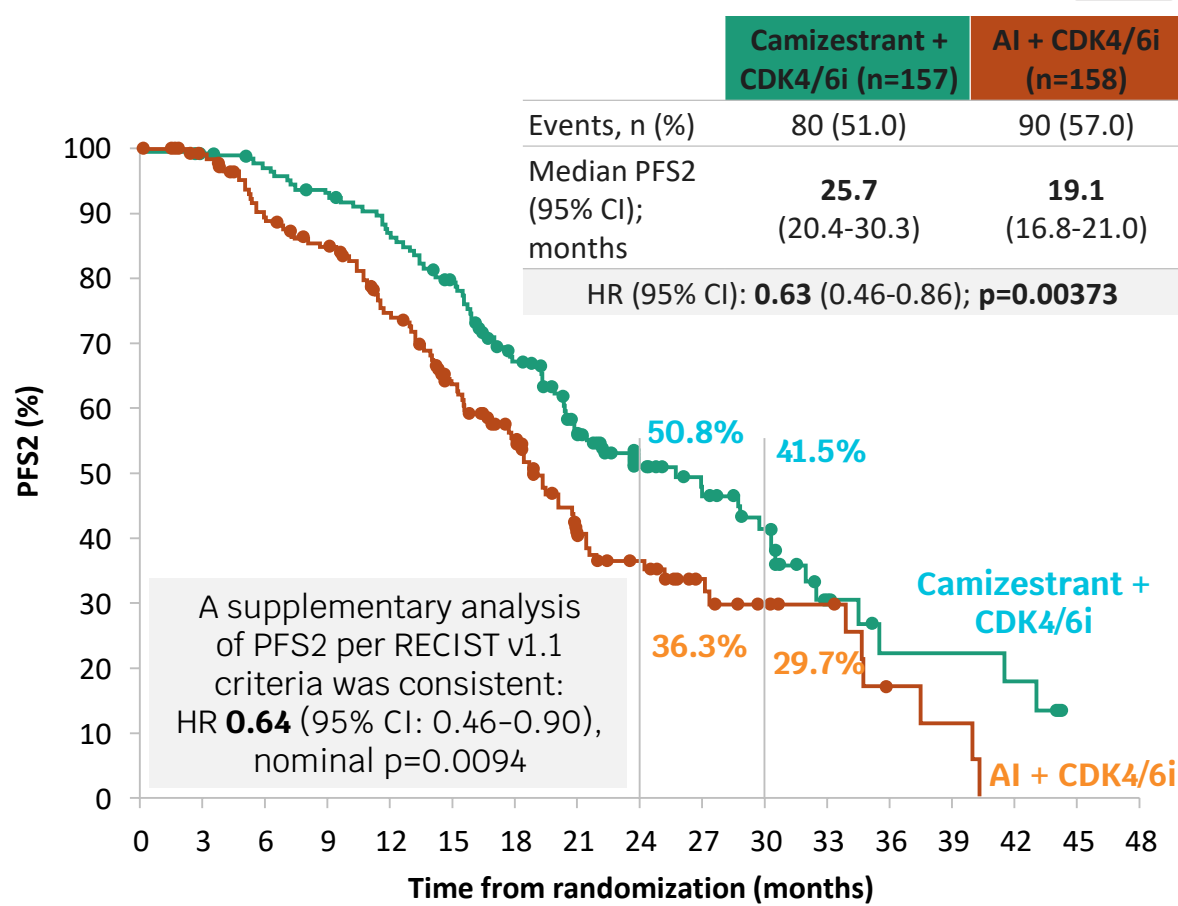
Updated PFS (primary endpoint, investigator-assessed)



Number of patients at risk

157	143	125	109	90	78	57	42	31	23	17	7	5	2	2	0
158	127	90	73	48	35	20	16	12	4	1	1	0	0	0	0

Final (PFS2)



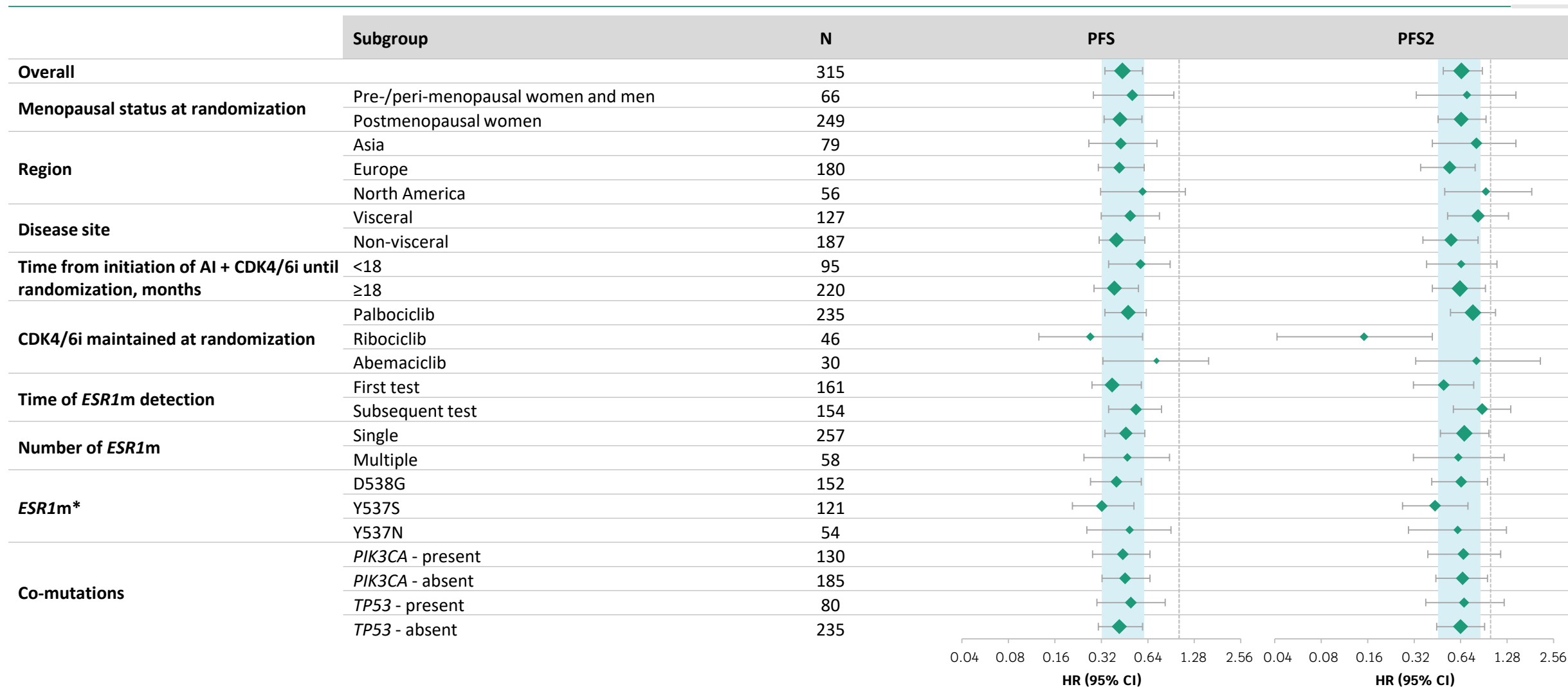
Number of patients at risk

157	150	145	138	127	113	86	63	42	32	24	10	5	5	4	0
158	149	129	120	102	82	60	40	30	17	12	8	3	2	0	0



SERENA6: Subgroup analysis PFS & PFS2

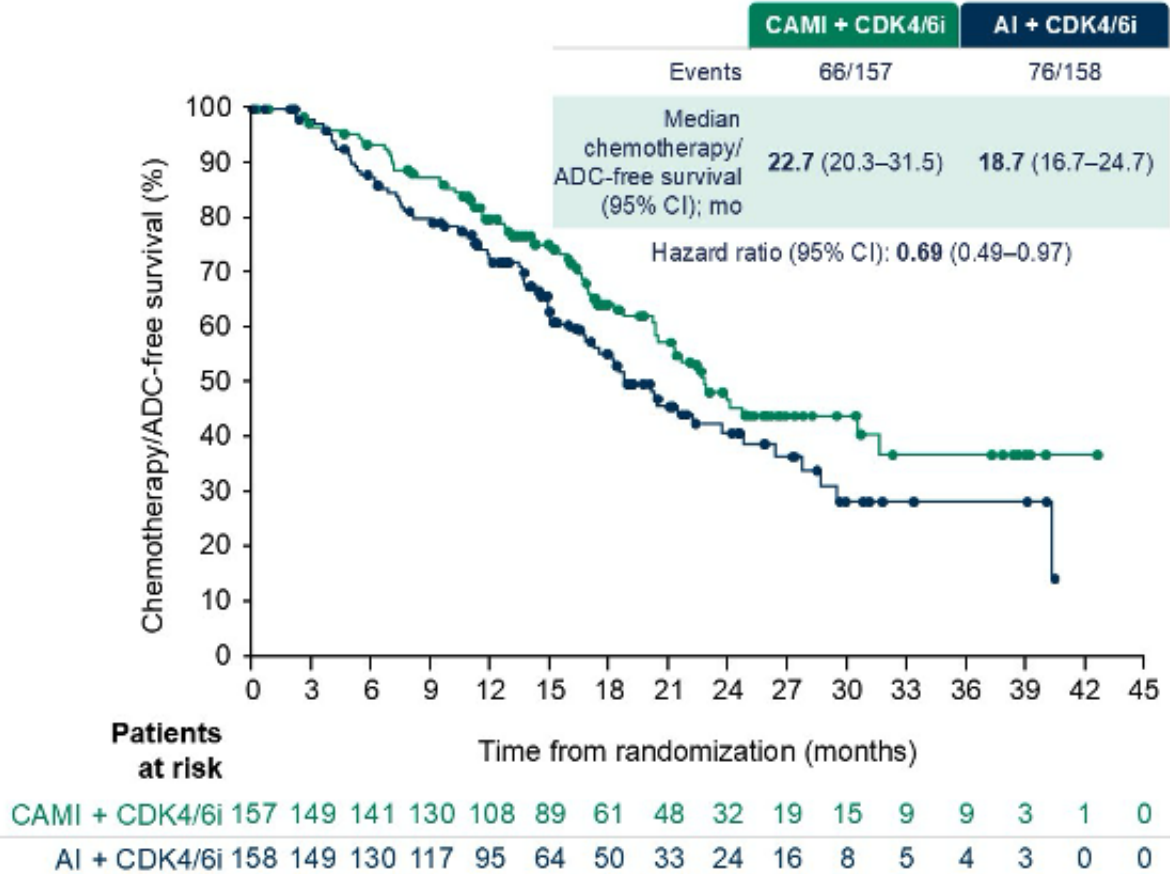
Consistent PFS and PFS2 benefit with camizestrant + CDK4/6i observed across subgroups



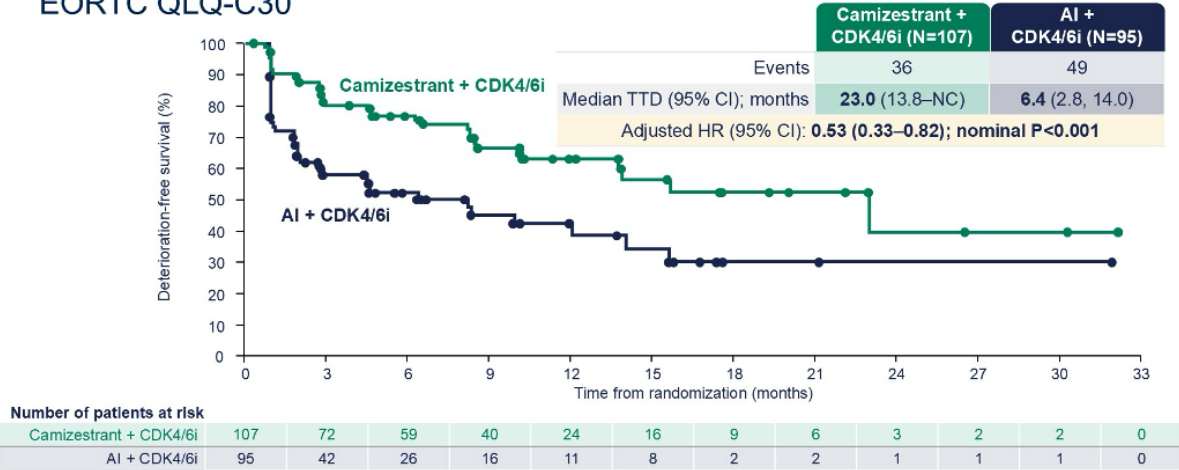
DCO3 (Jan 02, 2026). *The 3 most common ESR1m are shown



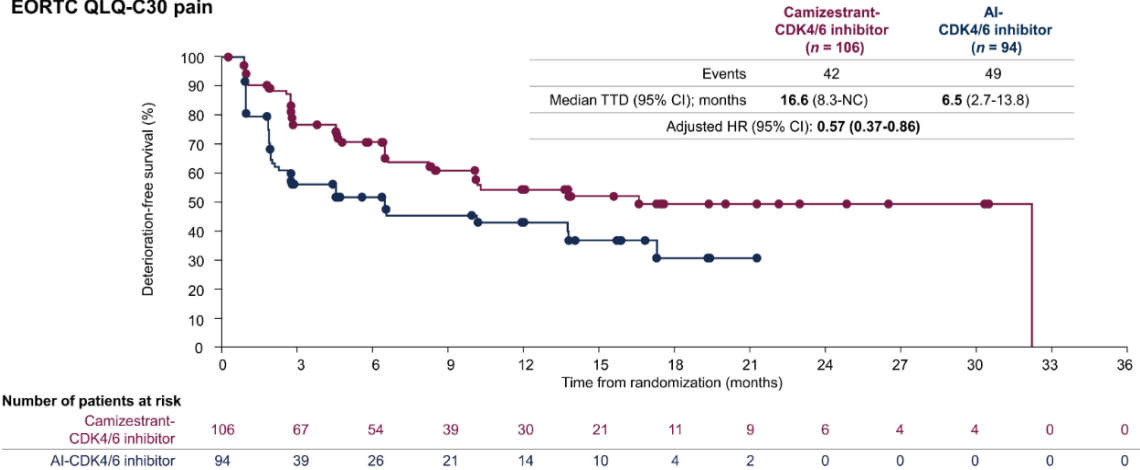
SERENA6: Switching to camizestrant + CDK4/6i prolongs chemotherapy/ADC-free survival, improves QOL



EORTC QLQ-C30



EORTC QLQ-C30 pain



Second pre-specified data cut off DC02: June 30, 2025.



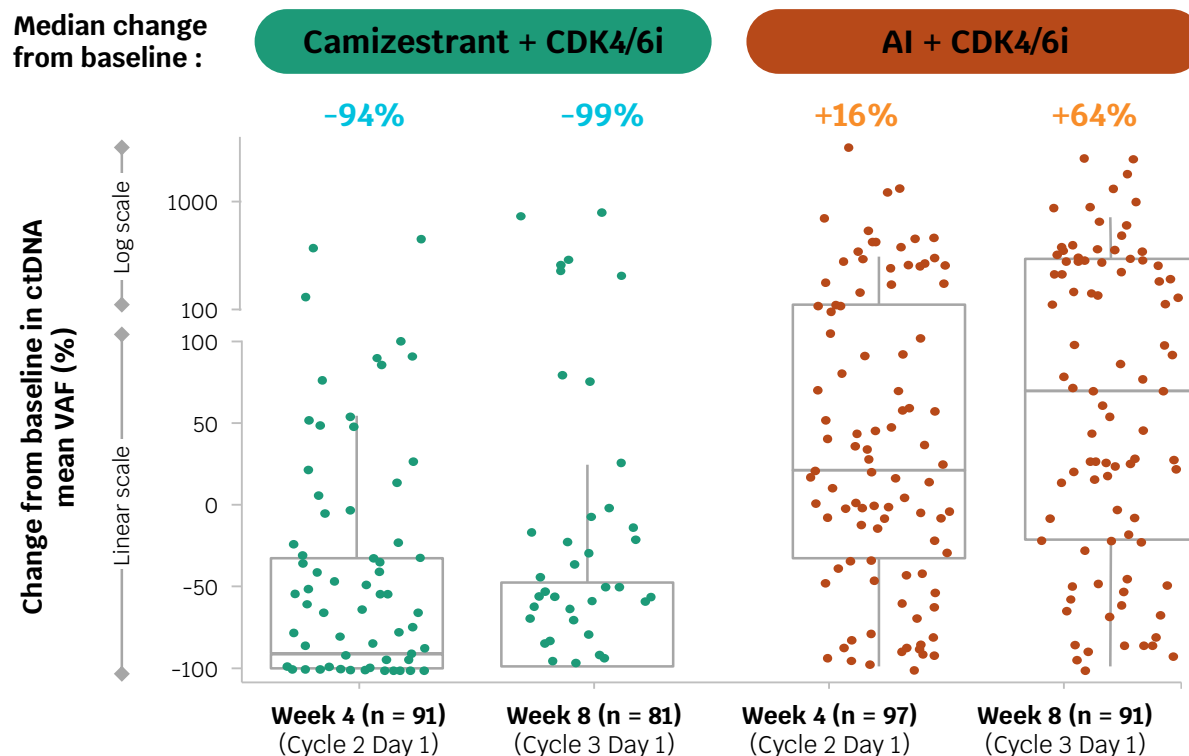
SERENA6: Total ctDNA dynamics on treatment

Total ctDNA levels were substantially reduced on camizestrant + CDK4/6i

Median 99% reduction at Week 8; 51% of patients showed clearance of total ctDNA

Change in total ctDNA

Median change from baseline :



Total ctDNA was **profoundly reduced** in the camizestrant + CDK4/6i arm vs the AI + CDK4/6i arm (Wilcoxon nominal $P < 0.00001$) at Week 4 and 8

Total ctDNA clearance by Guardant360*

Camizestrant +
CDK4/6i

51.0%

N = 50 / 98

AI + CDK4/6i

1.9%

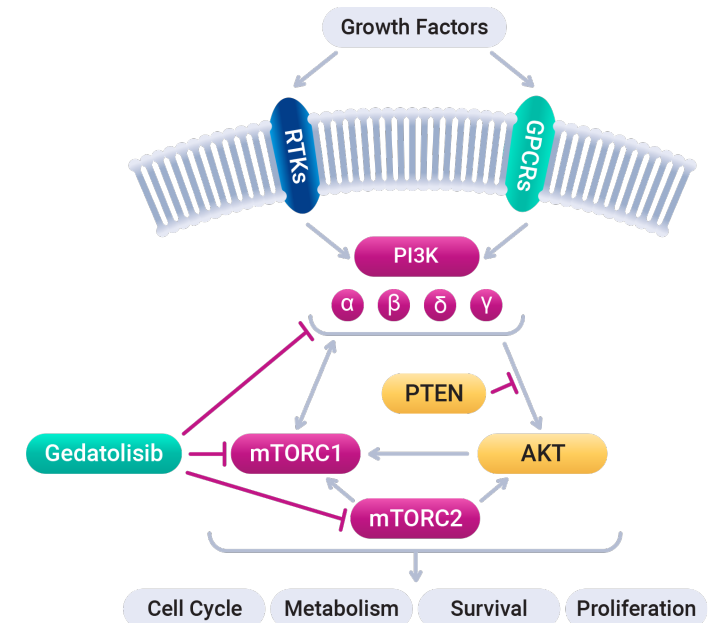
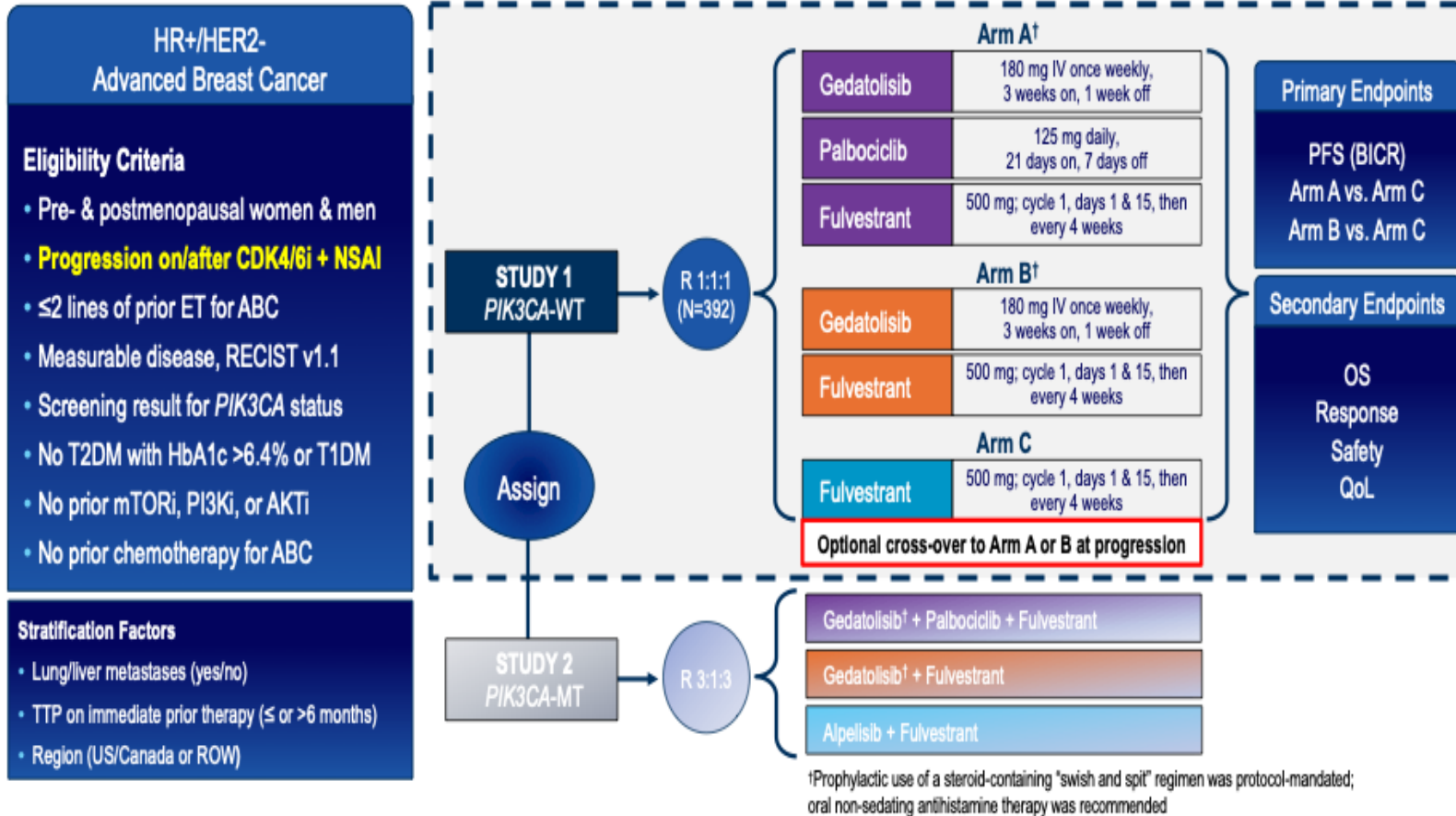
N = 2 / 108

In an exploratory analysis pooled across arms, total ctDNA clearance is associated with OS benefit (HR 0.39; 95% CI 0.19–0.73); consistent with other studies

Total ctDNA = mean VAF of probable tumor-specific somatic mutations (Guardant360); *Total ctDNA clearance at Week 4 and/or Week 8 in clearance-evaluable patients

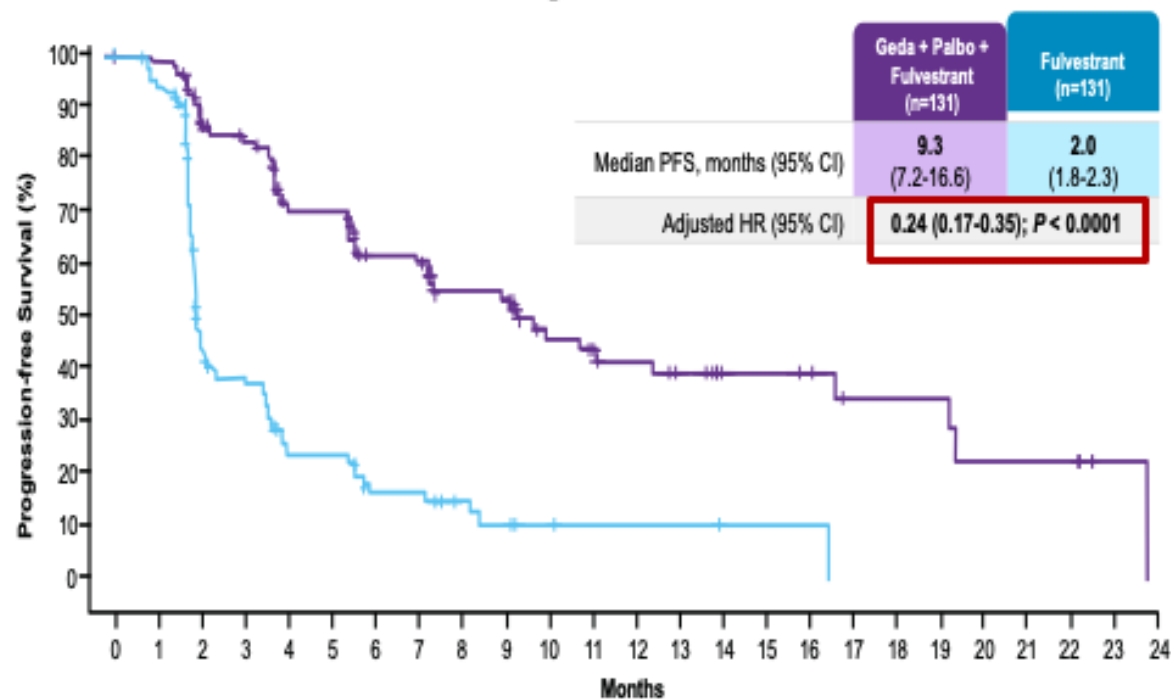


VIKTORIA-1

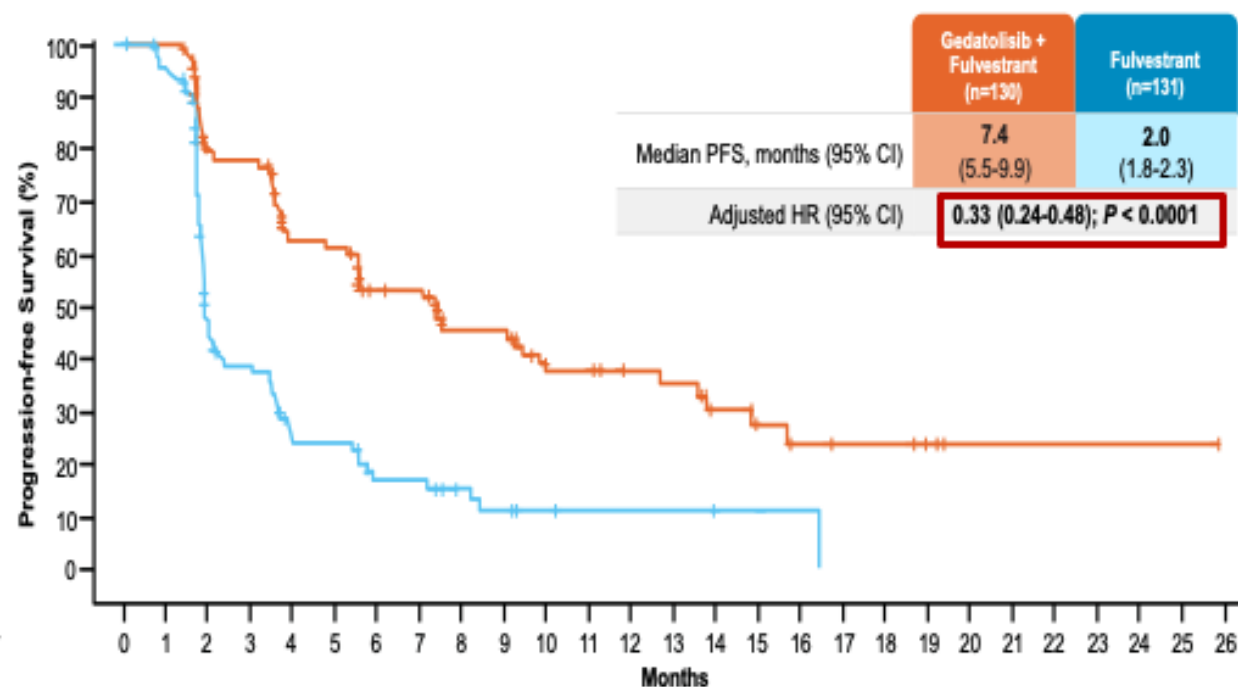


VIKTORIA-1: PFS in PIK3CA-wt (study 1)

“Triplet”



“Doublet”



Giredestrant + Fulvestrant, +/- palbociclib, FDA approved July 14, 2026 for patients with HR+/HER2- mBC, **PIK3CA-WT** following at least one line of ET in the metastatic setting

VIKTORIA-1: A randomized, open-label, Phase 3 study of gedatolisib + fulvestrant ± palbociclib vs. standard of care in HR+/HER2-/PIK3CA-mutant advanced breast cancer

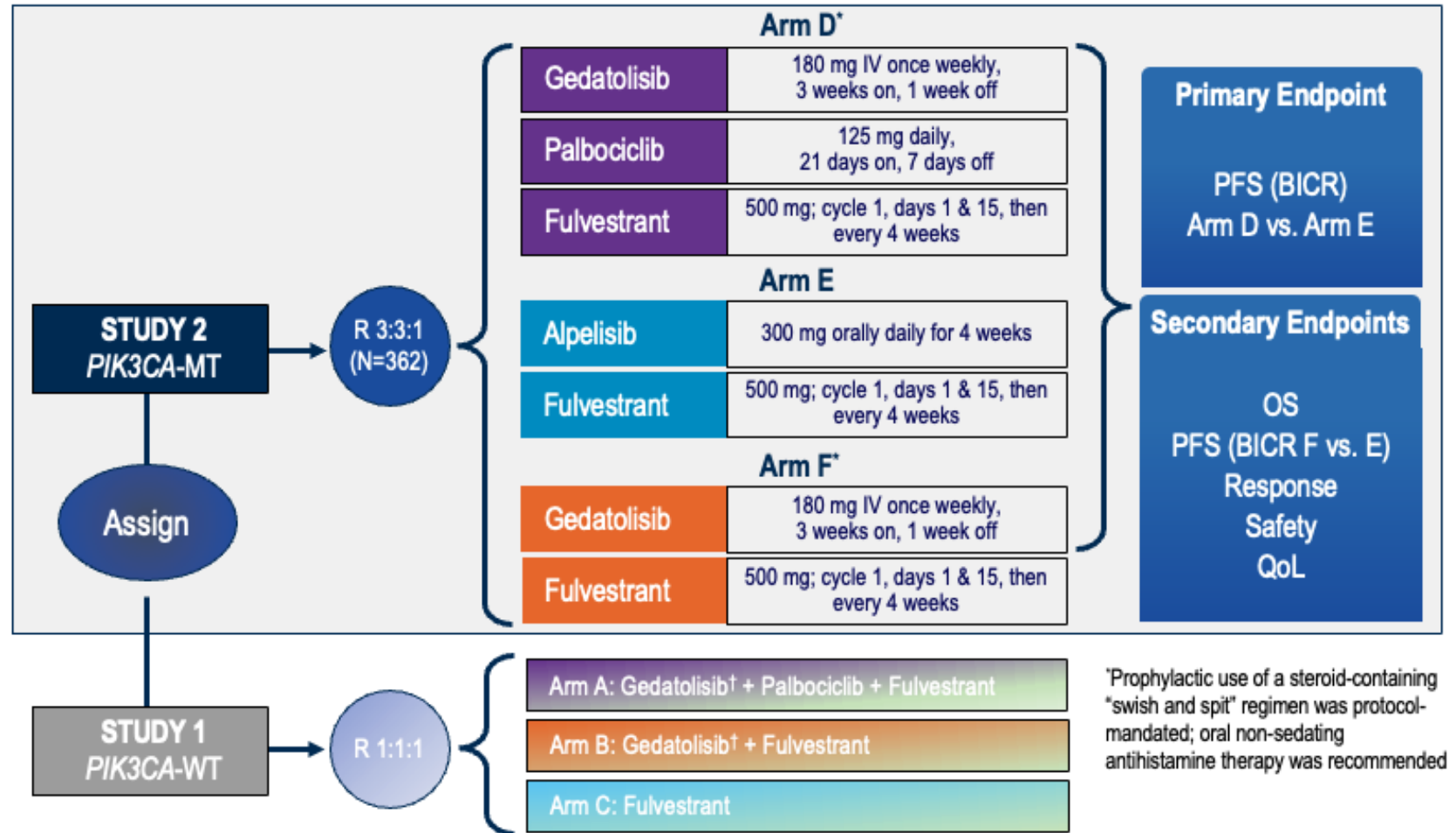
HR+/HER2- Advanced Breast Cancer

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

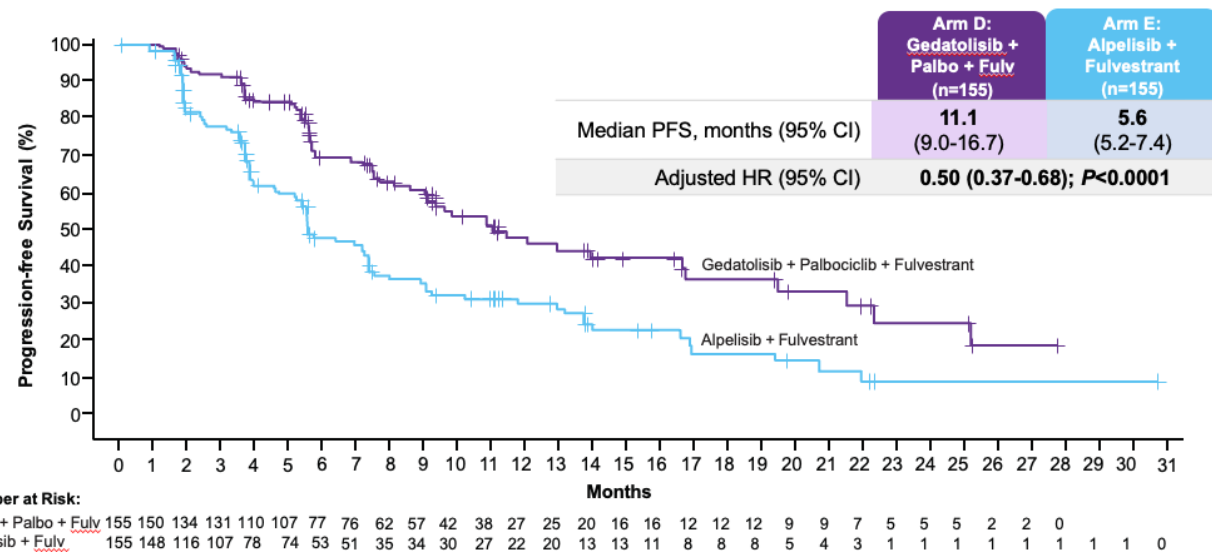
Stratification Factors

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



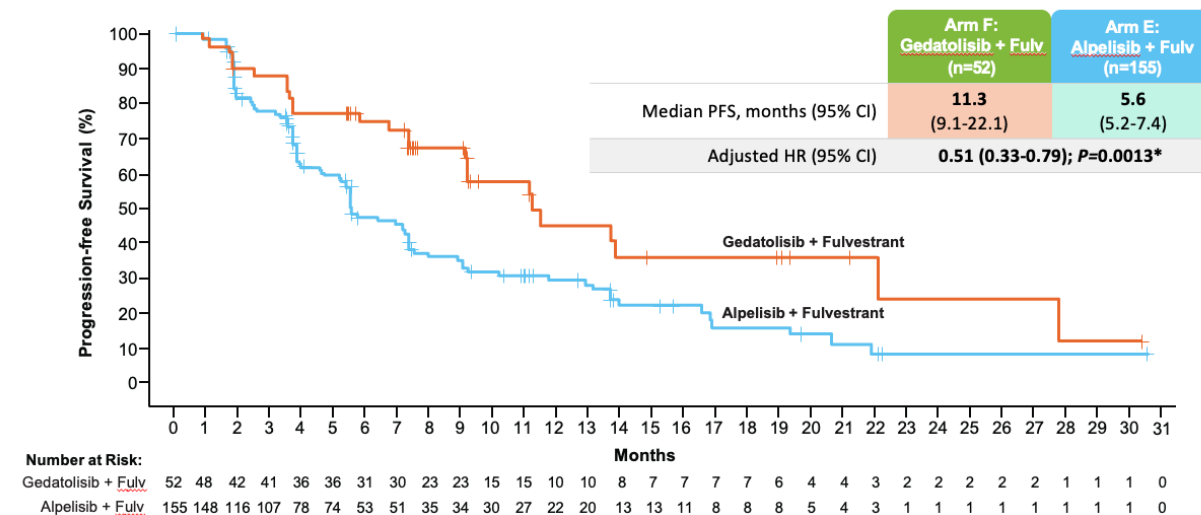
VIKTORIA-1: PIK3CA mut

Primary Endpoint: Progression-Free Survival (BICR) Gedatolisib Triplet vs. Alpelisib + Fulvestrant in VIKTORIA-1 Study 2



Secondary Endpoint: PFS (BICR)

Gedatolisib Doublet vs. Alpelisib + Fulvestrant in VIKTORIA-1 Study 2



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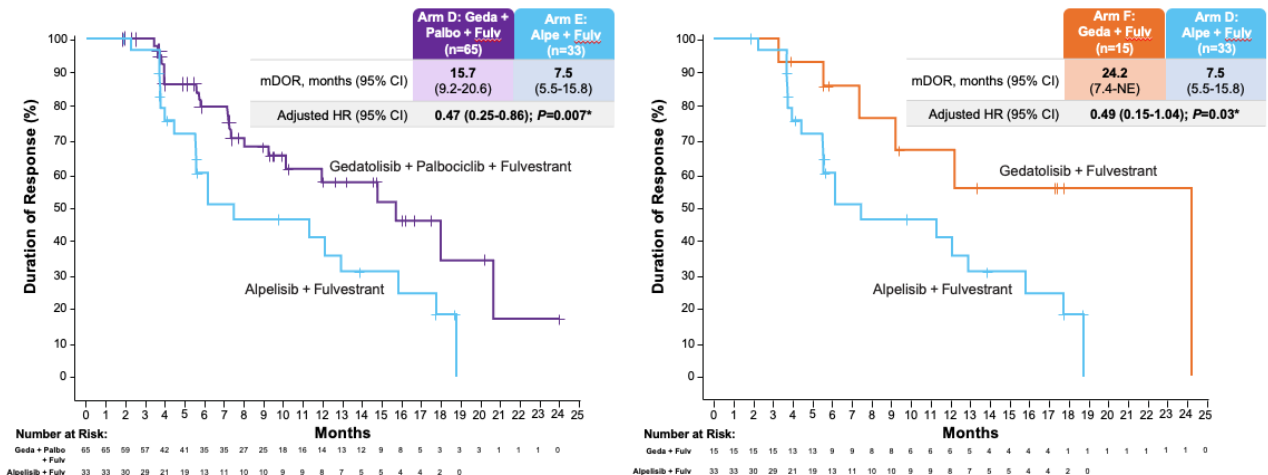


Safety/Toxicity

Exposure	Arm D: Gedatolisib + Palbociclib + Fulvestrant (n=153)			Arm F: Gedatolisib + Fulvestrant (n=52)			Arm D: Alpelisib + Fulvestrant (n=152)		
Median RDI, Geda (IQR)	93.3 (80.6-100)			100 (97.8-100)			--		
Median RDI, Alpe (IQR)	--			--			81.7 (64.8-96.2)		
TRAE and TR-SAE, n (%)									
Pts with ≥1 TRAE	150 (98.0)			50 (96.2)			147 (96.7)		
Study tx D/C for TRAE	4 (2.6)			2 (3.8)			11 (7.1)		
Pts with ≥1 TR-SAE	16 (10.5)			2 (3.8)			20 (13.2)		
Deaths due to TR-SAE*	1 (0.7)			0			2 (1.3)		
Adverse events, n (%)†	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Neutropenia‡	97 (63.4)	73 (47.7)	17 (11.1)	1 (1.9)	0	0	2 (1.3)	0	1 (0.7)
Stomatitis‡	94 (61.4)	25 (16.3)	0	32 (61.5)	3 (5.8)	0	52 (34.2)	8 (5.3)	0
Nausea	70 (45.8)	5 (3.3)	0	21 (40.4)	1 (1.9)	0	50 (32.9)	2 (1.3)	0
Rash‡	40 (26.1)	20 (6.5)	0	17 (32.7)	3 (5.8)	0	56 (36.8)	23 (15.1)	0
Vomiting	39 (25.5)	0	0	10 (19.2)	0	0	23 (15.1)	1 (0.7)	0
Fatigue	33 (21.6)	5 (3.3)	0	11 (21.2)	1 (1.9)	0	32 (21.1)	4 (2.6)	0
Diarrhea§	23 (15.0)	2 (1.3)	0	5 (9.6)	0	0	61 (40.1)	9 (5.9)	1 (0.7)
Hyperglycemia‡§	23 (15.0)	4 (2.6)	0	6 (11.5)	0	0	88 (57.9)	21 (13.8)	1 (0.7)

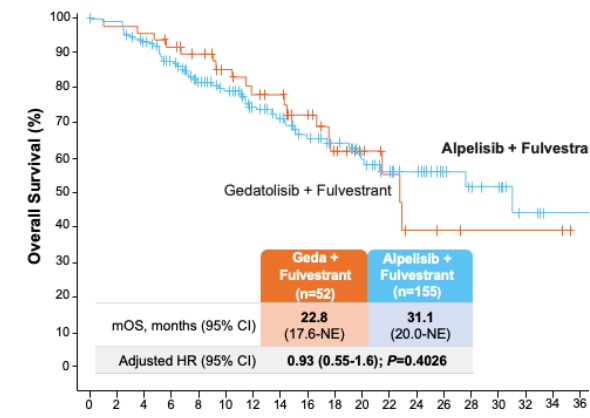
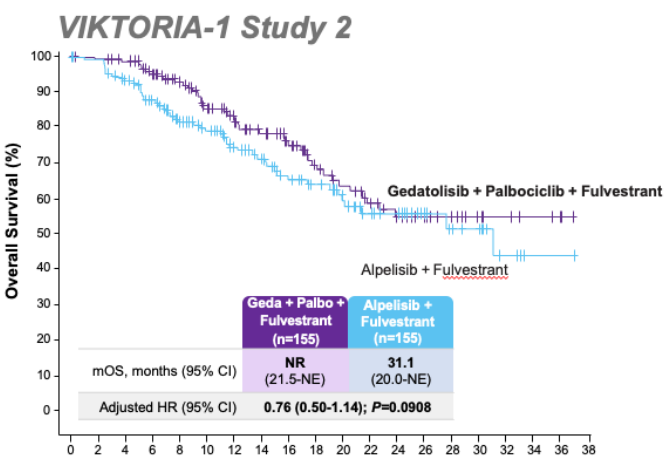
VIKTORIA-1: secondary endpoints and subgroup analysis

DoR:



OS:

Subgroup	Gedatolisib + Palbociclib + Fulvestrant n/N	Alpelisib + Fulvestrant n/N	Hazard Ratio (95% CI)
Age			
<65 years	53/107	65/97	0.47 (0.32-0.68)
≥65 years	15/48	15/48	0.46 (0.25-0.87)
Menopause status			
Pre/perimenopause	12/25	20/29	0.43 (0.18-0.84)
Postmenopause	54/126	79/126	0.50 (0.35-0.72)
Geographic area			
US/Canada	9/23	12/22	0.55 (0.23-1.28)
Rest of World	59/132	87/133	0.49 (0.35-0.69)
Presence of visceral metastasis			
Yes	54/117	81/118	0.52 (0.37-0.74)
No	14/38	18/37	0.38 (0.19-0.82)
Liver metastasis			
Yes	43/78	60/79	0.47 (0.31-0.70)
No	25/77	39/76	0.46 (0.28-0.78)
Lines of prior tx for ABC			
<2	63/143	86/134	0.50 (0.36-0.70)
≥2	5/12	13/21	0.47 (0.17-1.30)
TTP on immediate prior tx			
≤6 months	13/28	15/28	0.60 (0.28-1.27)
>6 months	55/127	84/127	0.45 (0.32-0.64)
Prior CDK4/6i for ABC			
Ribociclib	28/71	45/67	0.45 (0.28-0.71)
Palbociclib	32/64	40/66	0.59 (0.39-1.00)
Abemaciclib	10/25	18/28	0.35 (0.17-1.07)



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VIKTORIA-1 takeaways

Pan-PI3K + mTOR inhibition may drive benefit regardless of PIK3CA mutation status (WT and mut both benefit)

FDA approved for wild-type indication July 2026

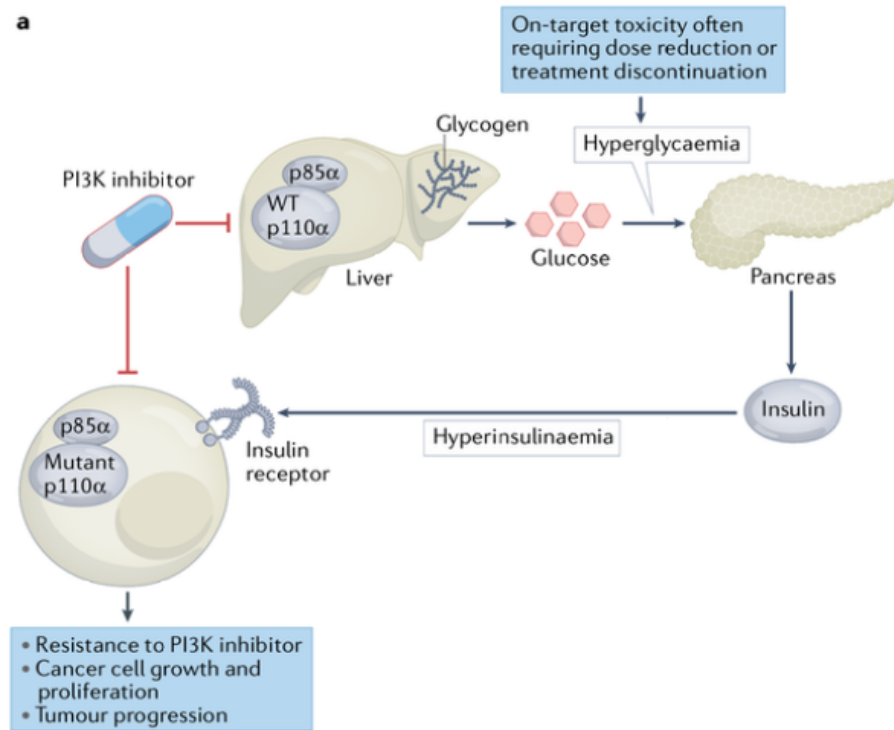
IV route – will it limit clinical use?

Subcutaneous route to come

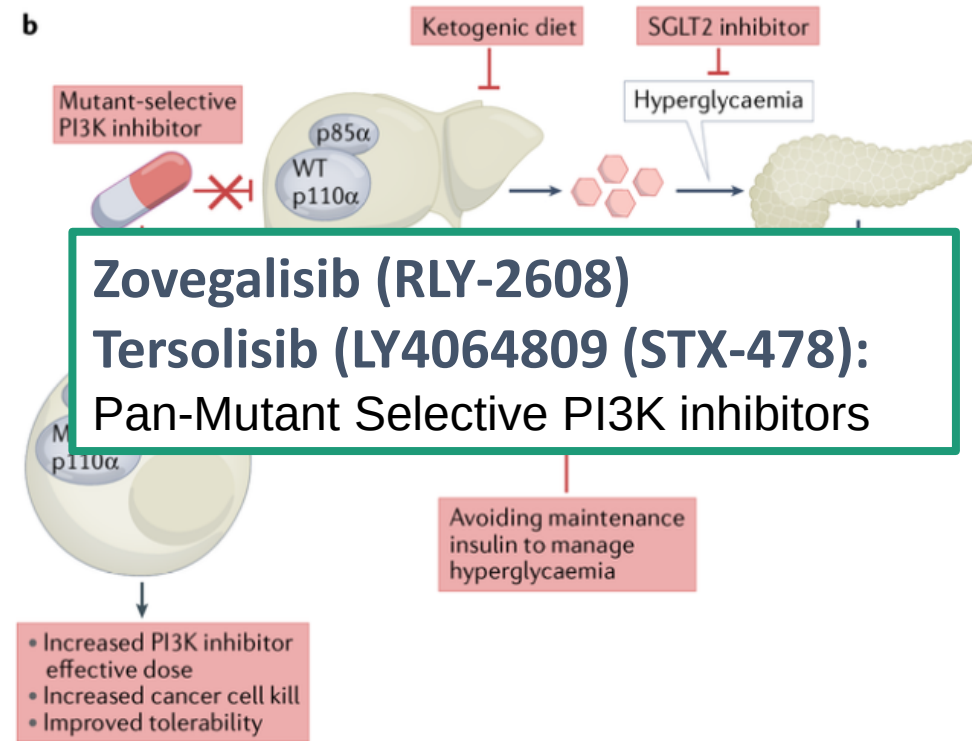
Encouragingly less hyperglycemia but still on-target side effects e.g. stomatitis, rash



Therapeutic Window



(a) Conventional PI3K Inhibitors



Zovegalisib (RLY-2608)
Tersolisib (LY4064809 (STX-478)):
Pan-Mutant Selective PI3K inhibitors

(b) Mutant-Selective PI3K Inhibitors

ReDiscover-2 – Phase III Registrational Trial for Post-CDK4/6 inhibitor HR+/HER2- Advanced Breast Cancer with a PIK3CA Mutation

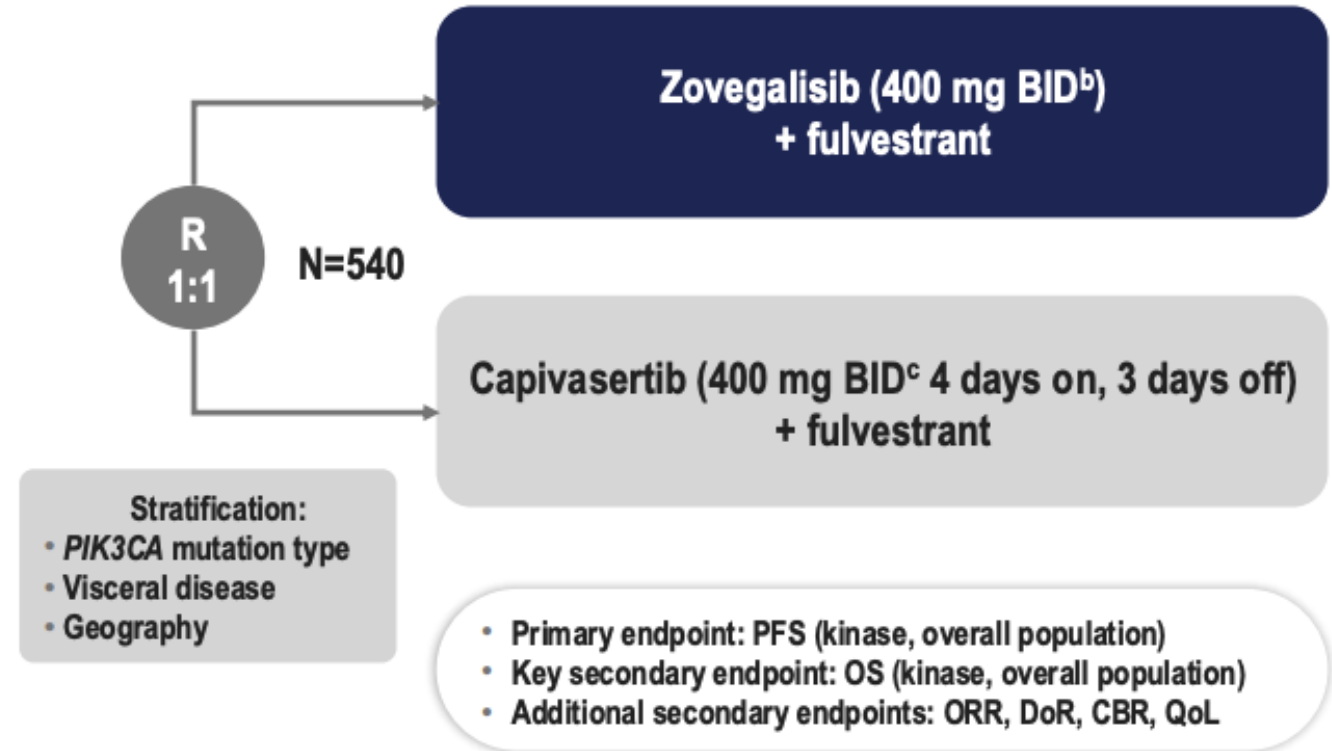
Key Eligibility Criteria:

Inclusion criteria

- *PIK3CA*-mutated HR+/HER2- ABC
- No concomitant *PTEN* or *AKT* tumor alterations
- Measurable disease or evaluable bone-only disease
- Progression in ABC or adjuvant^a setting on or after:
 - 1-2 lines ET, and
 - 1 line CDK4/6i

Exclusion criteria

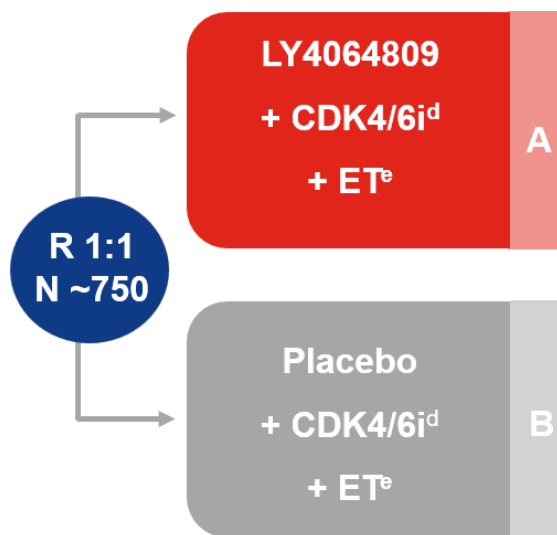
- Prior PI3Ki, AKTi, mTORi, ADC, IO, or investigational CDKi, CDK2i, CDK4i
- Progression on ≤6 mo ET-based regimen for ABC
- Type 1 diabetes, or type 2 diabetes requiring antihyperglycemic medication
- Fasting plasma glucose ≥140 mg/dL, or HbA1c ≥7.0% (≥53 mmol/mol)



A Phase 3, Randomized, Double-blind, Placebo-controlled Study of LY4064809 Combined with a CDK4/6 inhibitor and Endocrine Therapy in Adults with HR+, HER2- Advanced Breast Cancer with a *PIK3CA* Mutation who received no prior treatment for Advanced Breast Cancer (**PIKALO-2**)

1L *PIK3CA*-mutant^a HR+, HER2- aBC

- Men & pre/post-menopausal women
- HbA1c <8.0% & T2DM not requiring insulin allowed
- **Prior therapy: 0 for aBC**
Patients may be:
 - Newly diagnosed (de novo) aBC
 - Relapsed >12 months from completion of (neo)adjuvant ET ± CDK4/6i
 - Relapsed on or within 12 months from completion of (neo)adjuvant ET ± CDK4/6i^b



Primary endpoint:
Investigator-assessed PFS

- Key Secondary endpoints:**
- OS (key), BIRC-PFS, ORR, PK & PRO
 - Safety in the ITT population

All endpoints to be independently assessed in populations according to endocrine sensitivity^c

1. P1: Endocrine Sensitive (n=550)
2. P2: Endocrine Resistant (n=200)

Randomization within each Population Stratified by:

1. Physician's choice of CDK4/6i^d (abemaciclib/ribociclib/palbociclib)
2. Prior CDK4/6i (Y vs N)
3. Visceral metastases (Y vs N)



Key Takeaways: Metastatic Disease

What did we learn?

Oral SERDs/PROTACs are more effective than fulvestrant (and exemestane) in patients whose tumors have acquired *ESR1m*

This represents 35-40% of patients with HR+/HER2- MBC

Oral SERDs may be superior to standard endocrine therapy when combined with targeted agents *regardless of ESR1m status*

Overall toxicity is as expected from each individual agent

Ongoing studies to help define the role of this emerging strategy

Current state:

Option to switch AI to SERD at the emergence of *ESR1m*: Camizestrant

2nd line monotherapy therapy for patients with *ESR1m* and indolent highly endocrine responsive disease

Elacestrant, Imlunestrant, Vepdegestrant

And new combination option Imlunestrant + Abemaciclib

More combinations with targeted agents are on the horizon

Everolimus or Abemaciclib depending on co-morbidities, duration of response to prior CDK4/6i

Fulvestrant + PI3K/AKT/mTOR pathway agents continues to evolve (Gedatolisib)

Rapidly changing data and treatment options! 2026 is likely to see multiple approvals in this space



Looking to the future

Other endocrine therapies:
CERAN, SERCA

- CERAN, SERCA, SERMs

Moving oral SERD/CERAN to
first line?

- SERENA-4 (camizestrant), OPERA-02 (palazestrant), persevERA (giredestrant)

Innovations on targeted
partners:

- CDK2 inhibitors/degraders, CDK4 selective inhibitors, KAT6 inhibitors, RSK, Aurorakinase inhibitors, PI3K

Thank You

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