Hormone receptor-positive breast cancer

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Disclosures

I have served as an advisor for PUMA, Lilly, Pfizer, Seagen, Novartis, Astra-Zeneca and have served on DSMB for Gilead

All slides included in this presentation are publicly available at SABCS.org

Topics to cover

- Early stage disease
  - Disease outcomes based on race
  - Abemaciclib and everolimus as adjuvant therapies
- Metastatic disease
  - CDK 4/6 inhibition in visceral disease/crisis
  - CDK 4/6 inhibition through progression
  - Oral SERDS

San Antonio Breast Cancer Symposium®, December 6-10, 2022

Race and Clinical Outcomes in the RxPONDER Trial: A Clinical Trial Rx for Positive Node, Endocrine Responsive Breast Cancer (SWOG S1007)

Yara Abdou, William E Barlow, Julie R Gralow, Funda Meric-Bernstam, Kathy S Albain, Daniel F Hayes, Nancy U Lin, Edith A Perez, Lori J Goldstein, Stephen K Chia, Sukhbinder Dhesy-Thind, Priya Rastogi, Emilio Alba, Suzette Delaloge, Anne F. Schott, Steven Shak, Priyanka Sharma, Danika L. Lew, Jieling Miao, Joseph M. Unger, Debasish Tripathy, Lajos Pusztai, Gabriel N. Hortobagyi, Kevin Kalinsky

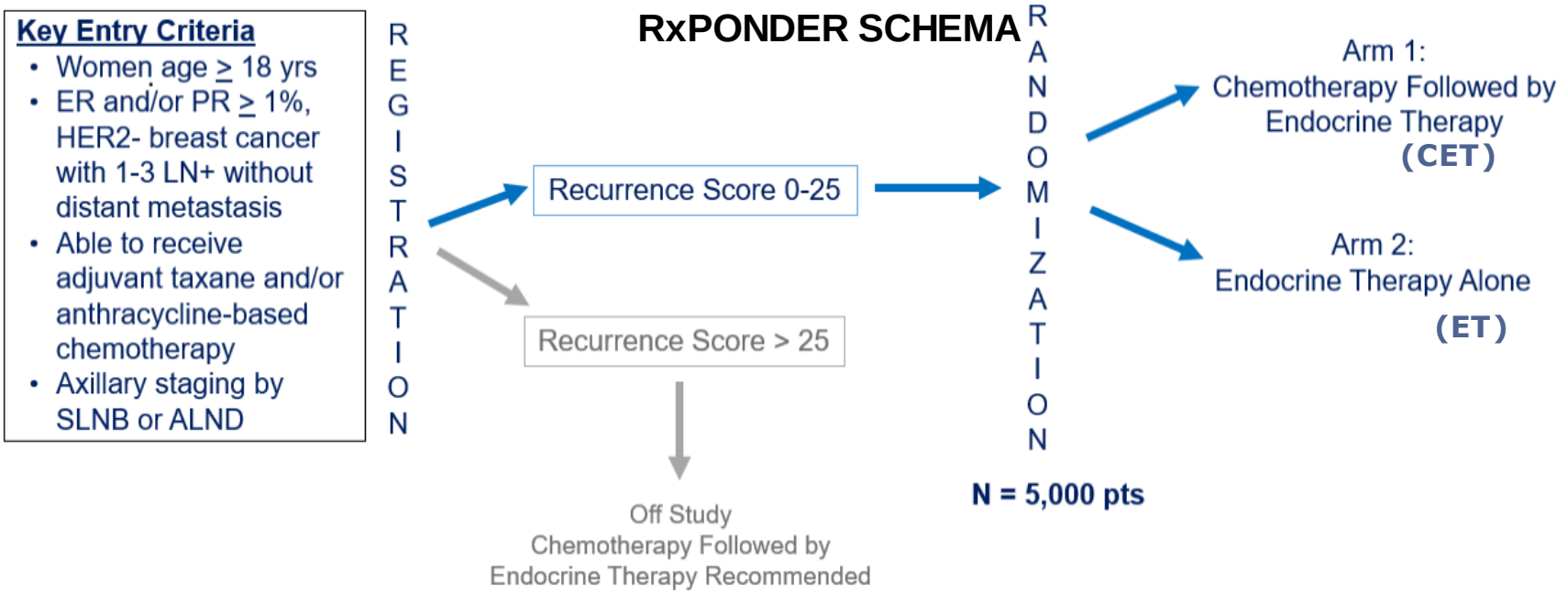
Background

- Racial disparities in breast cancer outcomes continue to be a major health care challenge.
- US Black women have 4% lower incidence of breast cancer, yet 40% higher breast cancer mortality than White women.
- Other studies have found that disparities persist even after adjustment for non-biological factors.
- We report an analysis of clinicopathologic characteristics, survival outcomes and race in association with Recurrence Score (RS) in participants (pts) in the RxPONDER trial.

Breast cancer statistics, ACS 2022; Albain, et al. JNCI 2021

Background

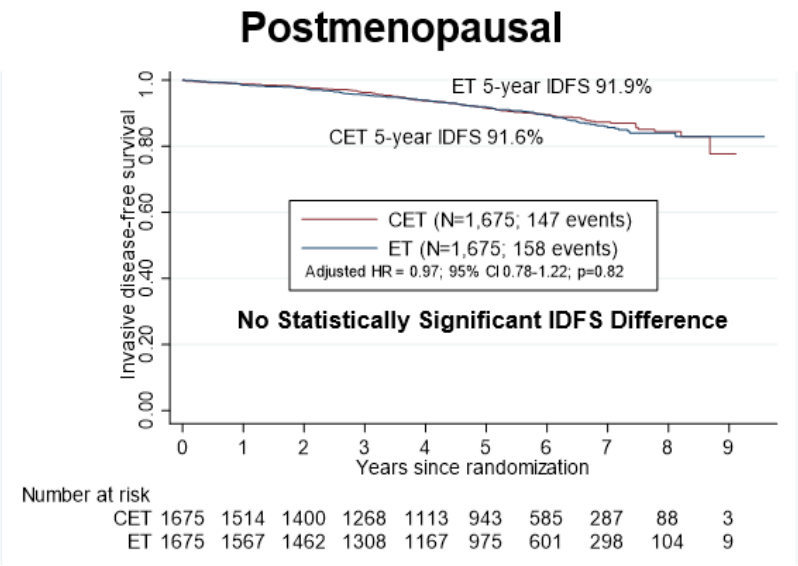
- RxPONDER: Clinical utility of the 21-gene RS in pts with HR+, HER2- breast cancer and 1-3 positive lymph nodes (1-3 LN+)

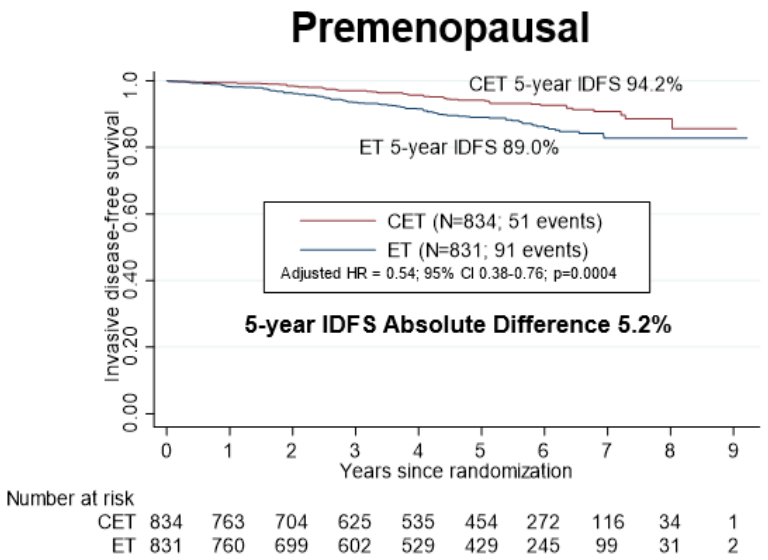


Kalinsky, et al. NEJM 2021

Background

- RxPONDER: Chemotherapy benefit differed by menopausal status:
  - Postmenopausal: no chemotherapy benefit for pts with RS ≤ 25
  - Premenopausal: chemotherapy benefit observed





Kalinsky, et al. NEJM 2021

Objectives

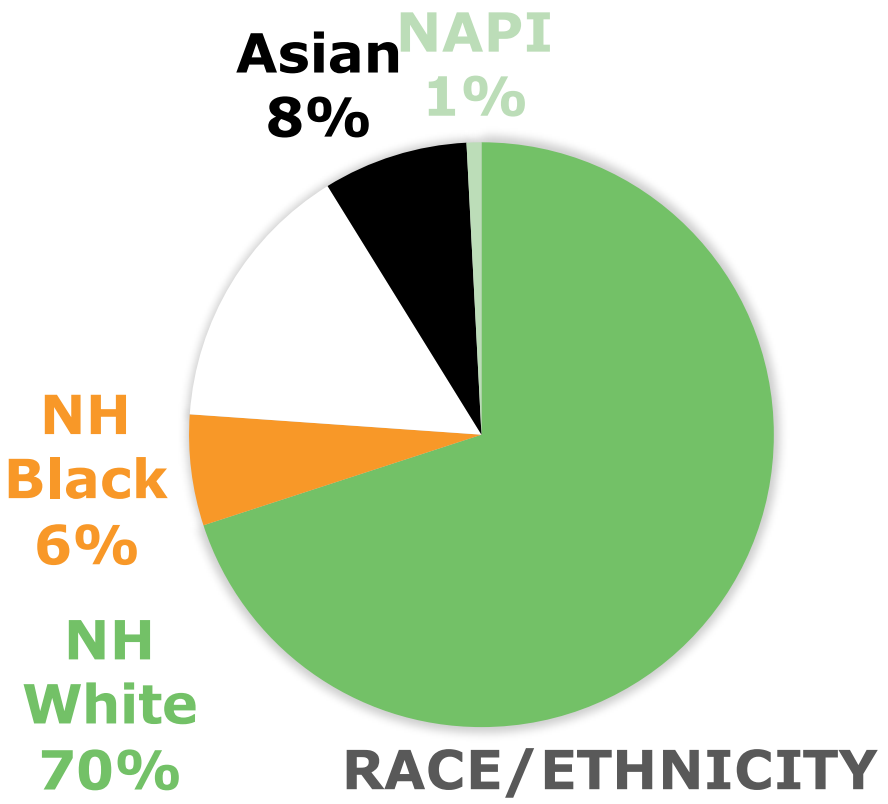
- Evaluate the entire cohort by race for:
  - Clinicopathologic characteristics
  - Recurrence Score distribution
- Analyze clinical outcomes by race using two endpoints: Invasive Disease-Free Survival (IDFS), Distant Relapse-Free Survival (DRFS)
- Determine if race is independently prognostic
- Determine whether race is predictive of treatment benefit

Abdou et al SABCS 2022.

Results

A total of **4,048** women with HR+/HER2- BC, 1-3 LN+, RS ≤ 25 and known race/ethnicity were included:

- 2,833 Non-Hispanic (NH) White pts (70%)
- 248 NH Black pts (6.1%)
- 610 Hispanic pts (15.1%)
- 324 Asian pts (8.0%)
- 33 NAPI pts (0.8%)



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Clinicopathologic characteristics by Race and Ethnicity

	NH White (n=2,833)	NH Black (n=248)	Asian (n=324)	NAPI (n=33)	Hispanic (n=610)
MEDIAN AGE (RANGE)	58 (28 – 87)	58 (18 – 86)	50 (28 – 76)	58 (42 – 74)	55 (28 – 79)
MENOPAUSAL STATUS					
Pre-menopausal	30%	23%	58%	27%	38%
Post-menopausal	71%	77%	42%	73%	62%
POSITIVE NODES					
1 node	66%	67%	73%	70%	65%
2 nodes	25%	22%	21%	24%	27%
3 nodes	9%	11%	6%	6%	9%
TUMOR SIZE					
T1	60%	55%	52%	64%	61%
T2	36%	41%	45%	36%	35%
T3	4%	3%	4%	0%	4%

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Clinicopathologic characteristics by Race and Ethnicity

	NH White (n=2,833)	NH Black (n=248)	Asian (n=324)	NAPI (n=33)	Hispanic (n=610)
RECURRENCE SCORE					
0-13	42%	42%	42%	39%	43%
14-25	58%	58%	58%	61%	57%
HISTOLOGIC GRADE					
Low	27%	22%	14%	15%	27%
Intermediate	62%	60%	79%	64%	58%
High	10%	18%	7%	21%	14%
BODY MASS INDEX					
< 20	4%	2%	13%	4%	3%
20-24	27%	6%	47%	23%	24%
25-29	31%	29%	32%	35%	35%
30-34	21%	27%	6%	12%	22%
35+	18%	35%	2%	27%	16%

distribute.

Abdou et al SABCS 2022.

Treatment type by Non-Hispanic White or Black Race

Primary Treatment Type among Women Randomized to Chemotherapy

	Anthracycline +/- Taxane	Taxane/ cyclophosphamide
Premenopausal NH White	187 (53%)	168 (47%)
Premenopausal NH Black	9 (33%)	18 (67%)
Postmenopausal NH White	261 (33%)	537 (67%)
Postmenopausal NH Black	26 (32%)	55 (68%)

*Endocrine therapy selection was similar for NH White and Black Race (data not shown)

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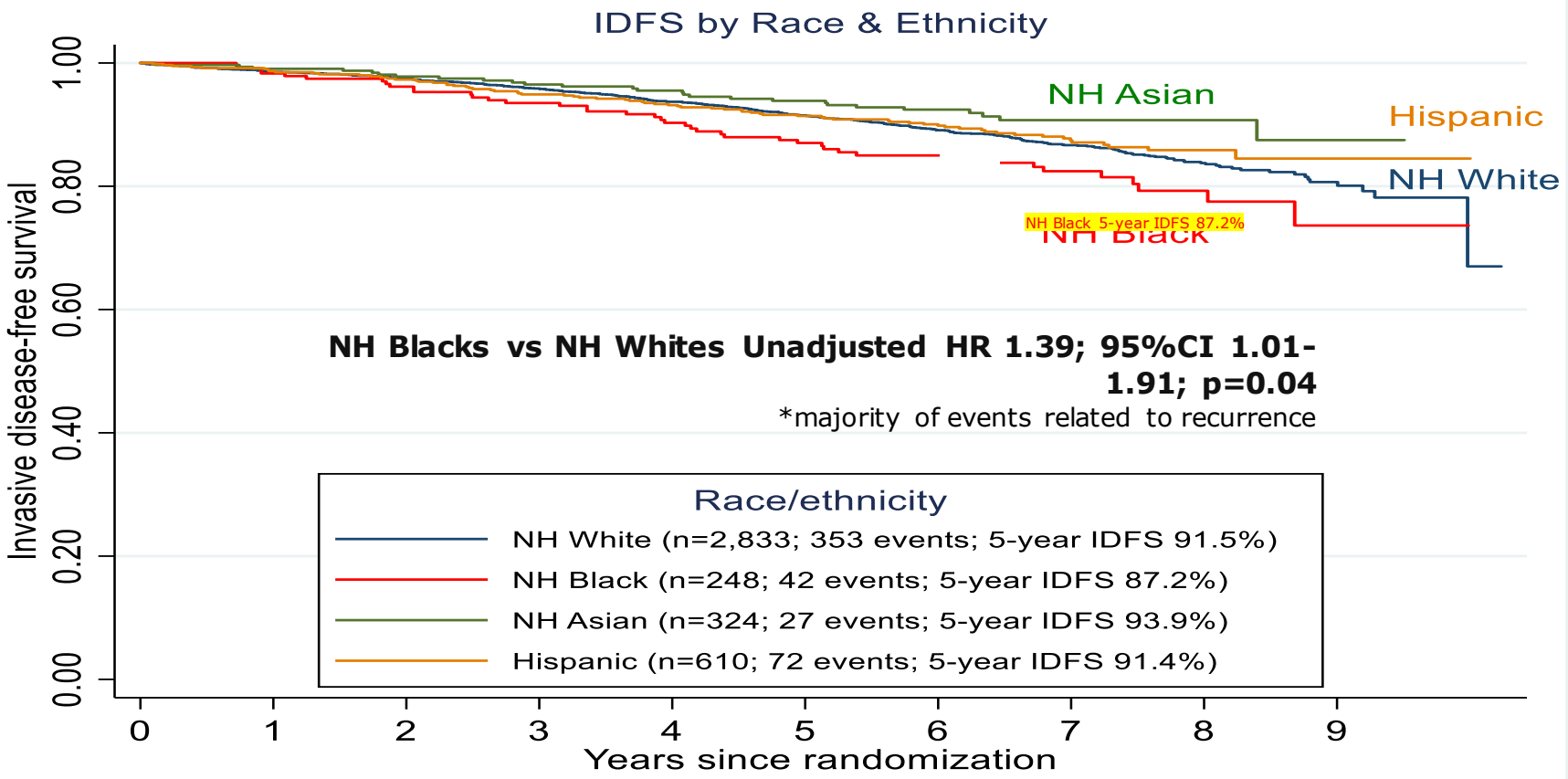
IDFS by Race and Ethnicity



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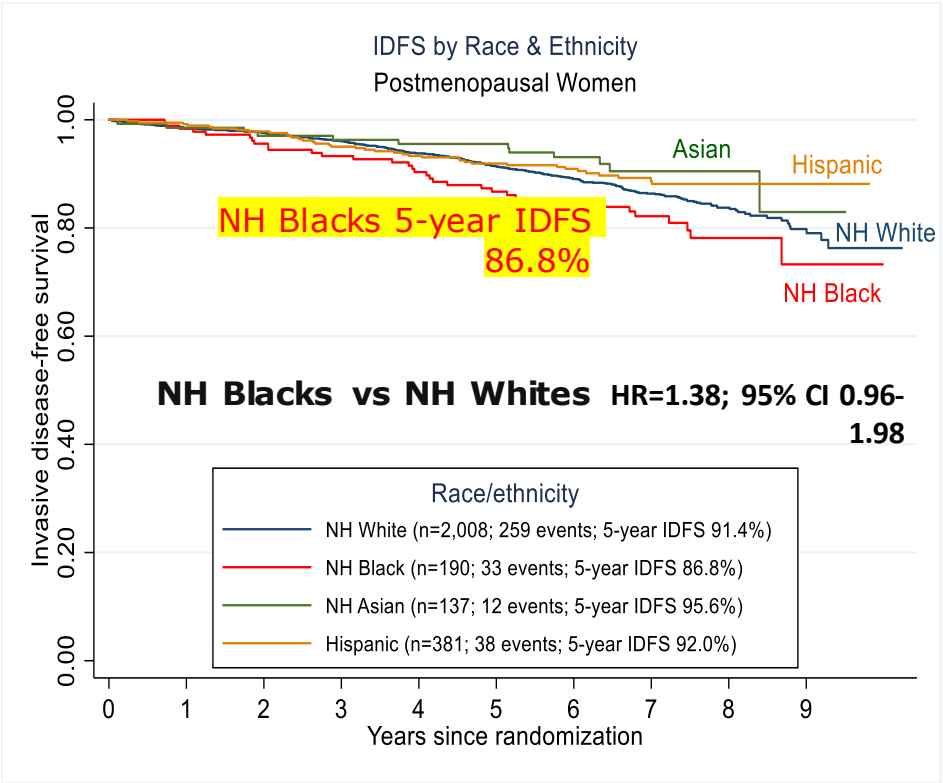
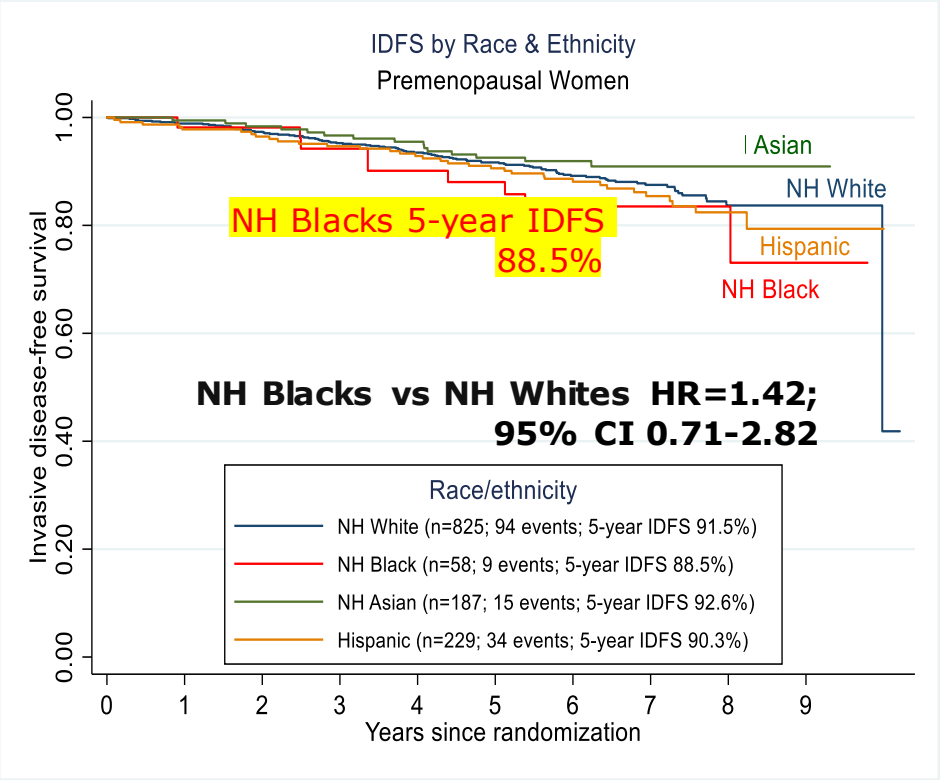
IDFS by Race/Ethnicity and menopausal status





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IDFS Multivariable Cox Regression for Race/Ethnicity

RACE	Adjusted Hazard Ratio (HR); 95% CI
NH Blacks vs NH Whites	HR=1.37; 95% CI 1.00-1.90; p=0.05
Asian vs NH Whites	HR=0.67; 95% CI 0.45-1.00; p=0.05
Hispanic vs NH Whites	HR=0.92; 95% CI 0.71-1.19; p=0.55

HR adjusted for RS, treatment arm, menopausal status, age, and grade

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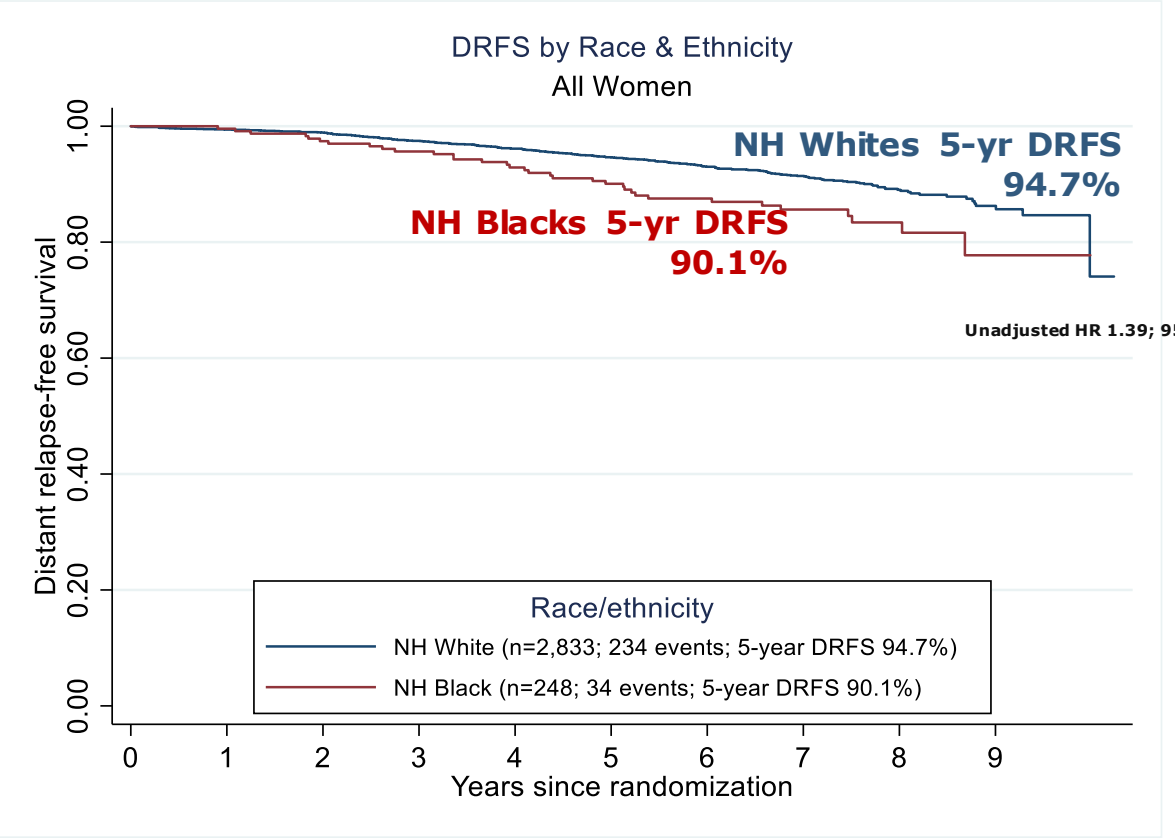
DRFS by NH White and Black Race



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DRFS Multivariable Cox Regression

RACE	Adjusted Hazard Ratio (HR); 95% CI
NH Blacks vs NH Whites	HR=1.71; 95% CI 1.19-2.45; p=0.004

HR adjusted for RS, treatment arm, menopausal status, age, and grade

RACE	Adjusted Hazard Ratio (HR); 95% CI
NH Blacks vs NH Whites	HR=1.31; 95% CI 0.81-2.10; p=0.27

HR adjusted for RS, treatment arm, menopausal status, age, grade and BMI

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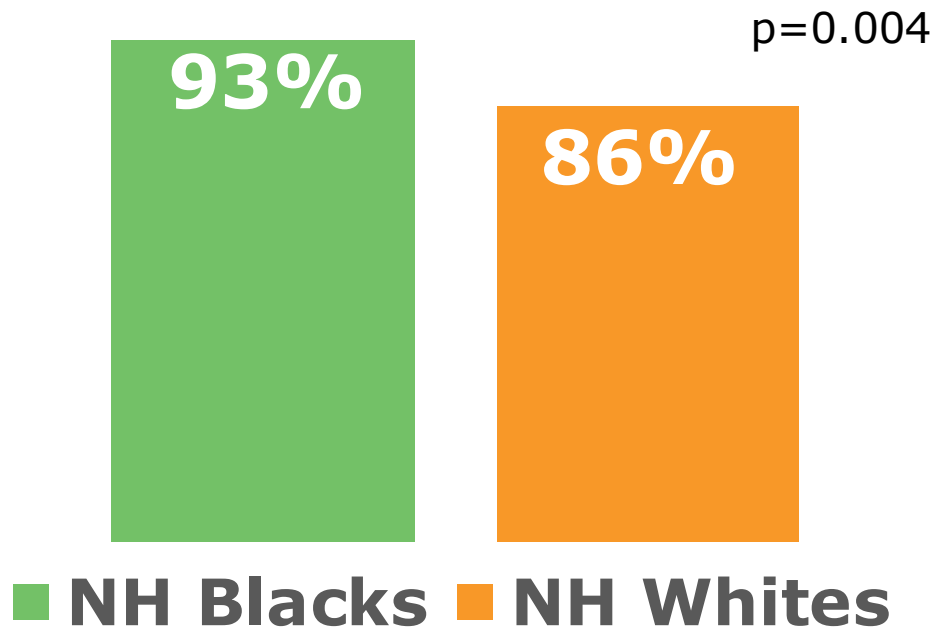
Accepted Treatment Assignment



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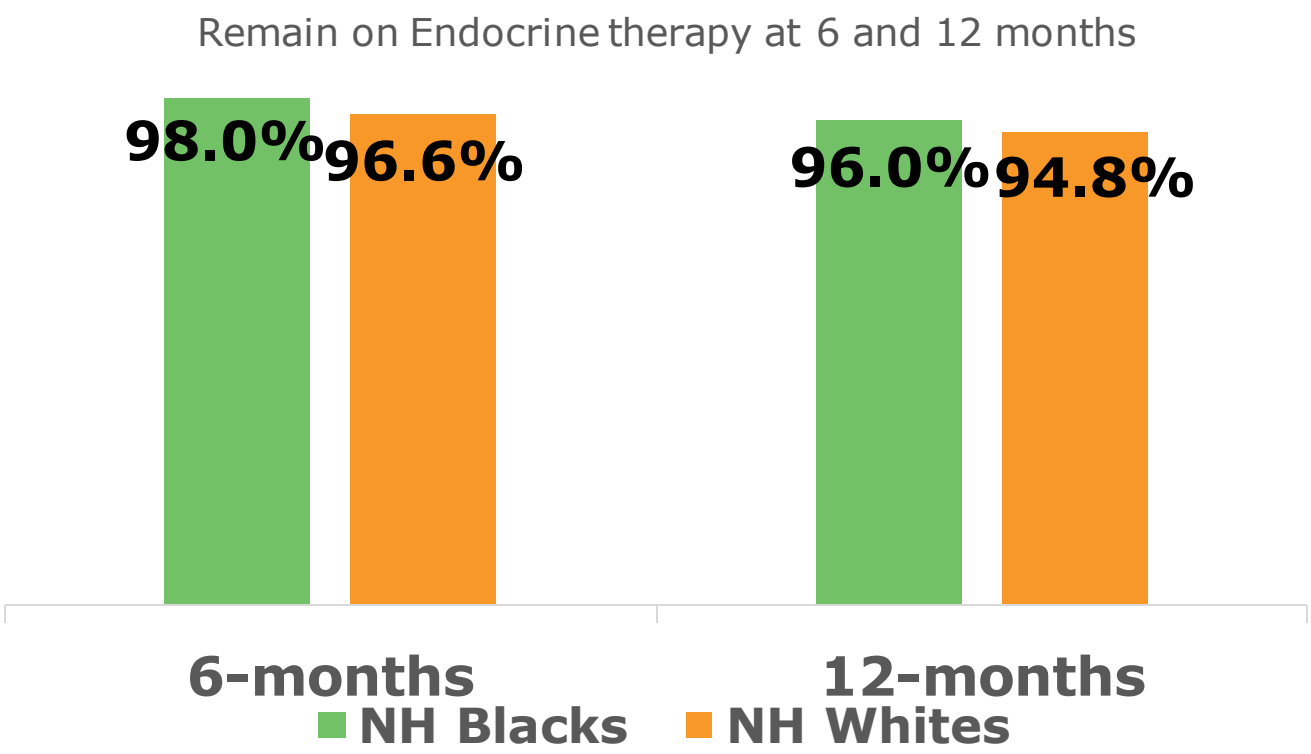
Endocrine Therapy Adherence



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RxPONDER Conclusions

- NH Black women with HR+/HER2- BC, 1-3 LN+ and RS ≤ 25 have worse outcomes compared to NH White women independent of RS, treatment arm, age and grade. Although, adjusting for BMI appears to decrease this effect.

- At this time definitive conclusions about racial differences in treatment benefit cannot be made due to the limited number of events in the NH Black cohort.

- NH Blacks were more likely to accept treatment assignment compared to NH Whites and were just as likely to remain on ET at 6 and 12-months. These data suggest that the outcome differences are less likely attributable to lack of treatment compliance within the first year. Longer follow up and further analysis is needed to confirm this finding.

Results from a phase III randomized, placebo-controlled clinical trial evaluating adjuvant endocrine therapy +/- 1 year of everolimus in patients with high-risk hormone receptor-positive, HER2-negative breast cancer: SWOG S1207

Mariana Chavez-MacGregor, Jieling Miao, Lajos Pusztai, Matthew P. Goetz, Priya Rastogi, Patricia A. Ganz, Eleftherios P. Mamounas, Soonmyung Paik, Hanna Bandos, Wajeeha Razaq, Anne O'Dea, Virginia Kaklamani, Andrea L.M. Silber, Lisa E. Flaum, Eleni Andreopoulou, Joseph Baar, Albert G. Wendt, Jennifer F. Carney, Priyanka Sharma, Julie R. Gralow, Danika L. Lew, William E. Barlow, Gabriel N. Hortobagyi.

Rationale

Dysregulation in the PI3kinase/AKT/mTOR signaling pathway is associated with endocrine therapy (ET) resistance.

Everolimus, an mTOR-inhibitor, in combination with ET prolonged PFS compared to ET alone among patients with metastatic hormone receptor (HR)-positive, HER2-negative breast cancer (BC)

- The previously reported UNIRAD trial evaluated everolimus in the adjuvant setting. The study did not meet its primary endpoint.

S1207 is a phase III randomized, placebo-controlled trial evaluating the role of everolimus in combination with ET in the adjuvant setting among patients with high-risk HR+ receptor-positive, HER2-negative BC. (NCT01674140).

Inclusion Criteria

Eligible patients:

- >18 years of age
- Histologically confirmed invasive HR-positive and HER2-negative high-risk BC
- All included patients received chemotherapy
- Four high- risk groups were defined as:
  - 1) Tumor ≥ 2cm node-negative disease (or pN1mi), and either an Oncotype DX® Recurrence Score (RS) > 25 or MammaPrint® high-risk category (MP high)
  - 2) 1-3 positive nodes and either RS >25, MP high or a pathological grade 3 tumor
  - 3) ≥4 positive lymph nodes
  - 4) neoadjuvant chemotherapy and residual disease with ≥1 lymph node involvement

Patients were randomized 1:1 to physician's choice adjuvant ET in combination with one year of everolimus (10 mg PO daily) or ET plus placebo stratified by risk group.

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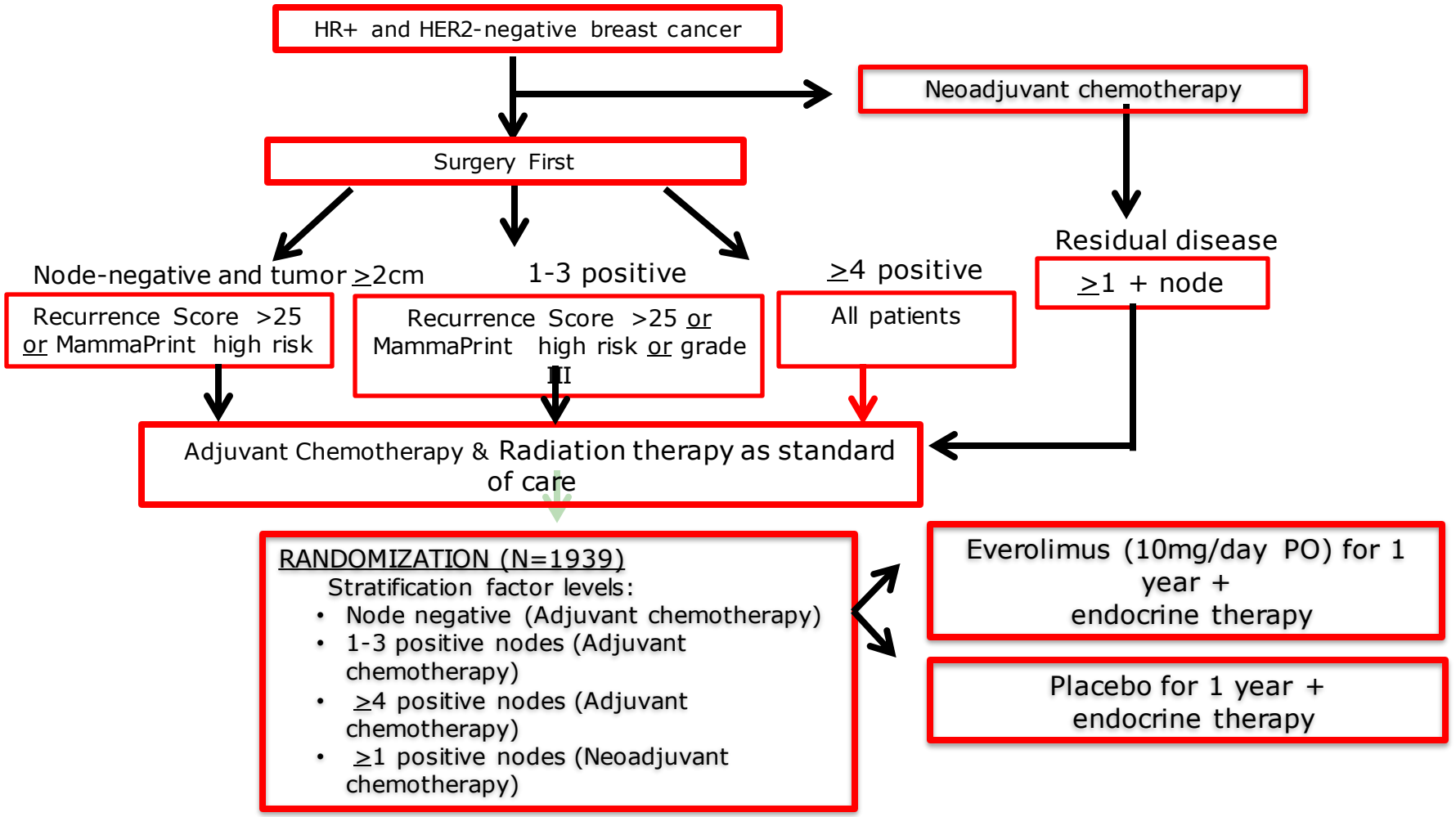
S1207 Study Design



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Statistical Considerations

Original design:

90% power to detect a hazard ratio of 0.75.

Sample size = 3500

Predicted risk membership

1. 45% (node negative high risk)
2. 35% (1-3 node positive high risk)
3. 15% (4+ positive nodes)
4. 5% (residual disease)

Revised design:

- 80% power to detect a hazard ratio of 0.75.
- Sample size = 1900
- Predicted risk membership
  1. 10% (node negative high risk)
  2. 10% (1-3 node positive high risk)
  3. 60% (4+ positive nodes)
  4. 20% (residual disease)

Change in design

- Changed April 2016 to reflect actual risk distribution
- No outcome information was used to change the design

Final analysis

- Planned at 219 IDFS events in the control arm or 3 years after last randomization
- Actual 211 IDFS events in the control arm

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Baseline Characteristics	TOTAL (n=1792)	PLACEBO (n=896)	EVEROLIMUS (n=896)
Age			
median (Range)	54 (22, 86)	54 (22, 85)	54 (26, 86)
Race			
White	1529 (85%)	757 (84%)	772 (86%)
Black	107 (6%)	58 (6%)	49 (5%)
Asian	64 (4%)	33 (4%)	31 (3%)
Other	263 (15%)	139 (16%)	124 (14%)
Hispanic	169 (9%)	82 (9%)	87 (10%)
Risk Group			
Node negative (Adjuvant chemotherapy)	158 (9%)	79 (9%)	79 (9%)
1-3 positive nodes (Adjuvant chemotherapy)	213 (12%)	107 (12%)	106 (12%)
≥4 positive nodes (Adjuvant chemotherapy)	710 (40%)	357 (40%)	353 (39%)
≥1 positive nodes (Neoadjuvant chemotherapy)	711 (40%)	353 (39%)	358 (40%)
Menopausal Status			
Pre-Menopausal	571 (32%)	290 (32%)	281 (31%)
Post-Menopausal	1221 (68%)	606 (68%)	615 (69%)

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Treatment Summary

REASON OFF TREATMENT	TOTAL (n=1792)	PLACEBO (n=896)	EVEROLIMUS (n=896)
Treatment Completed as Planned	1079 (60%)	651 (73%)	428 (48%)
Adverse Event (AE) or Side Effect	421 (23%)	86 (10%)	335 (37%)
Refusal Unrelated to AE	163 (9%)	84 (9%)	79 (9%)
Progression/Relapse	64 (4%)	43 (5%)	21 (2%)
Death	2 (0.1%)	1 (0.1%)	1 (0.1%)
Other- not specified	63 (4%)	31 (3%)	32 (4%)

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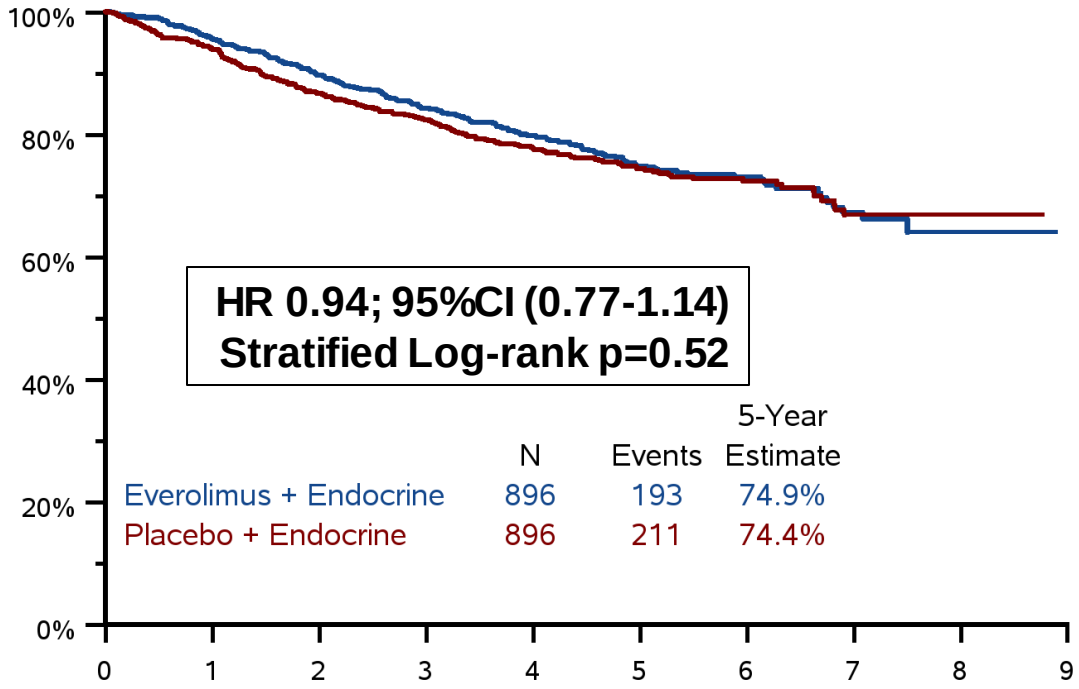
Primary Endpoint – IDFS



Patients at Risk										
Everolimus + Endocrine	896	760	694	619	476	315	185	72	12	0
Placebo + Endocrine	896	782	708	641	483	333	180	71	15	0

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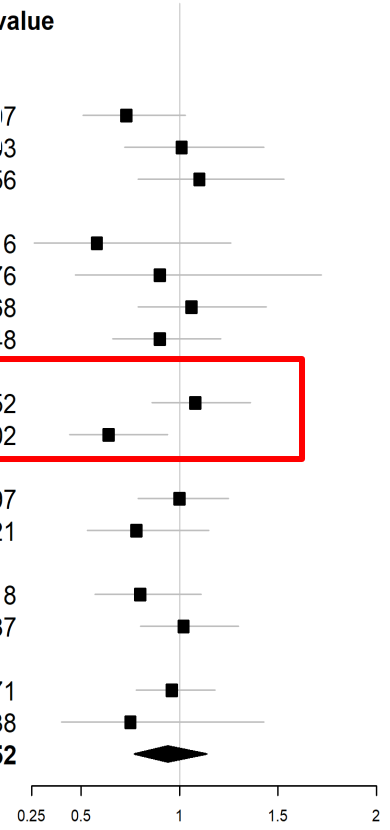
Primary Endpoint – IDFS: Subgroup analyses

	Placebo Events/N	Everolimus	IDFS HR (95% CI)	P-value
Age				
Age < 50	77/339	55/333	0.73 (0.51,	7
Age 50 -59	64/286	67/303	1.01 (0.72,	3
Age 60+	70/271	71/260	1.1 (0.79,	0.56
Risk Group				
RiskGroup1	17/79	10/79	0.58 (0.26,	0.16
RiskGroup2	19/107	18/106	0.9 (0.47,	0.76
RiskGroup3	85/357	86/353	1.06 (0.79,	0.68
RiskGroup4	90/353	79/358	0.9 (0.66,	0.48
Menopausal Status				
Post-Menopausal	144/606	149/615	1.08 (0.86,	0.52
Pre-Menopausal	67/290	44/281	0.64 (0.44,	0.02
Baseline Tamoxifen				
Not received	155/673	143/653	1 (0.79,1	0.97
Received	56/223	50/243	0.78 (0.53,	0.21
Baseline AI				
Not received	74/296	67/322	0.8 (0.57,	0.18
Received	137/600	126/574	1.02 (0.8,	0.87
Baseline Ovarian Suppression				
Not received	187/781	177/796	0.96 (0.78,	0.71
Received	24/115	16/100	0.75 (0.4,	0.38
Overall	**211/896**	**193/896**	**0.94 (0.77,**	**0.52**



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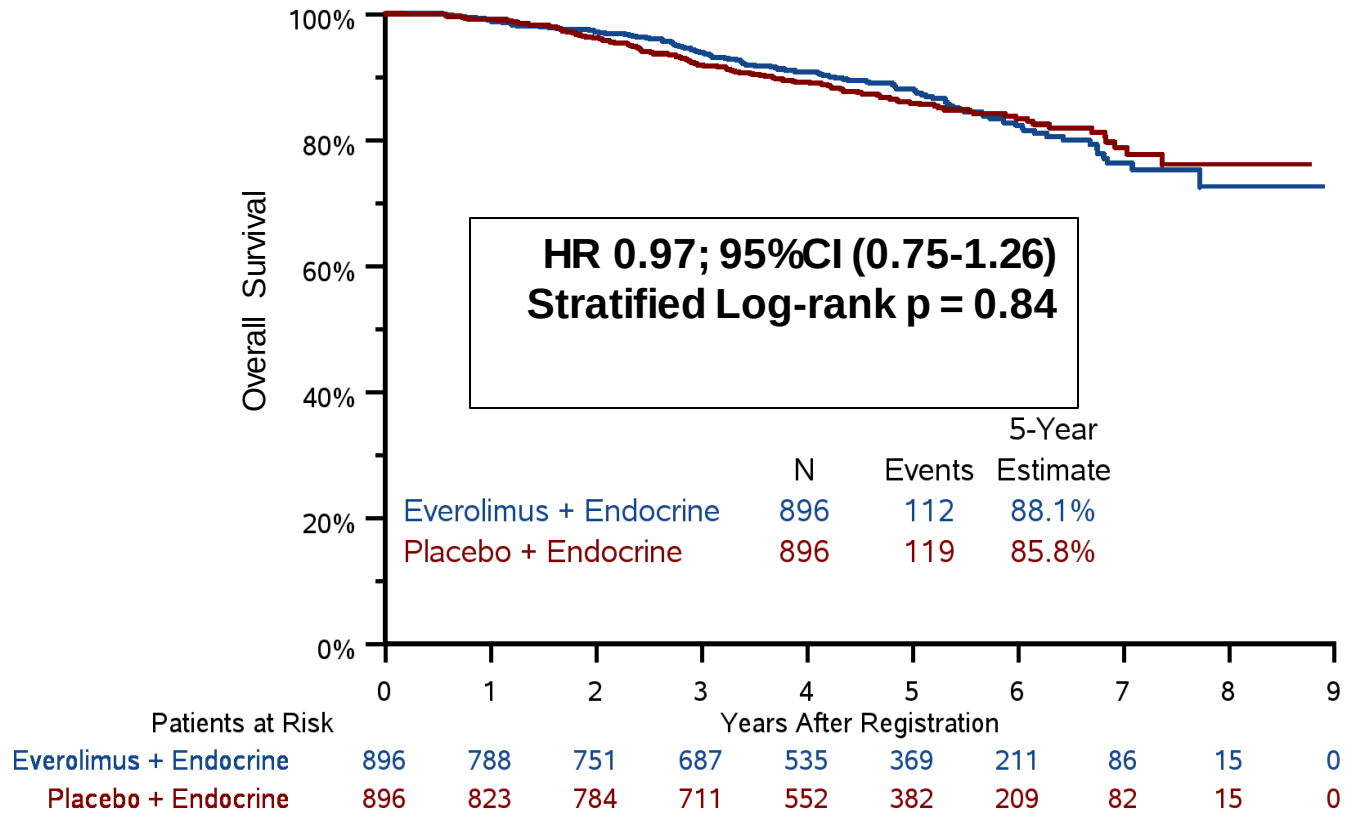
Secondary Endpoint- OS



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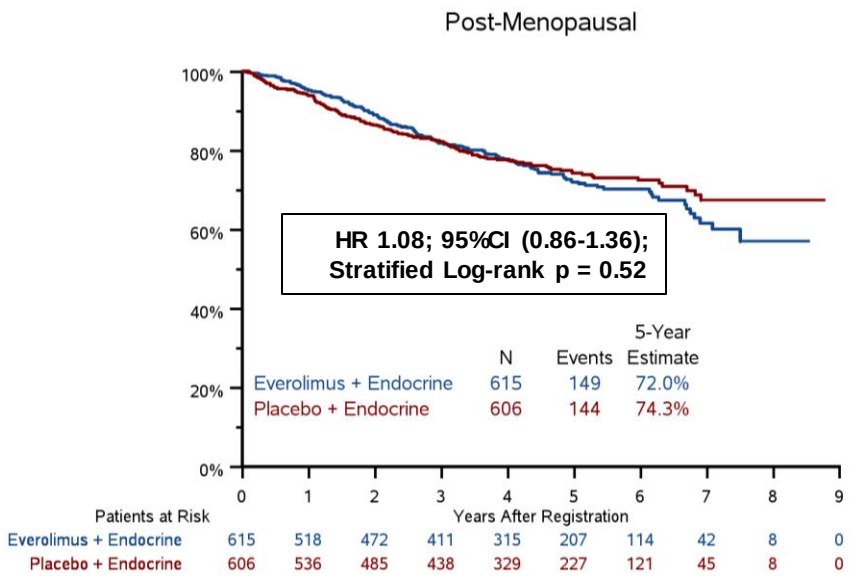
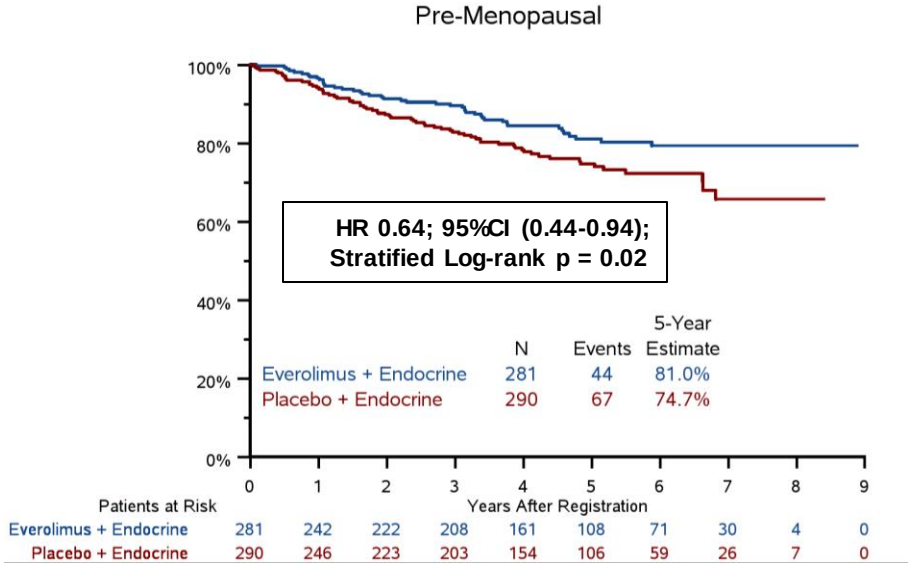
Exploratory Analysis by Menopausal Status- IDFS





COX REGRESSION MODEL	HR	95% CI	p-value
Treatment arm x Menopausal status Interaction	1.67	1.07-2.60	0.0241

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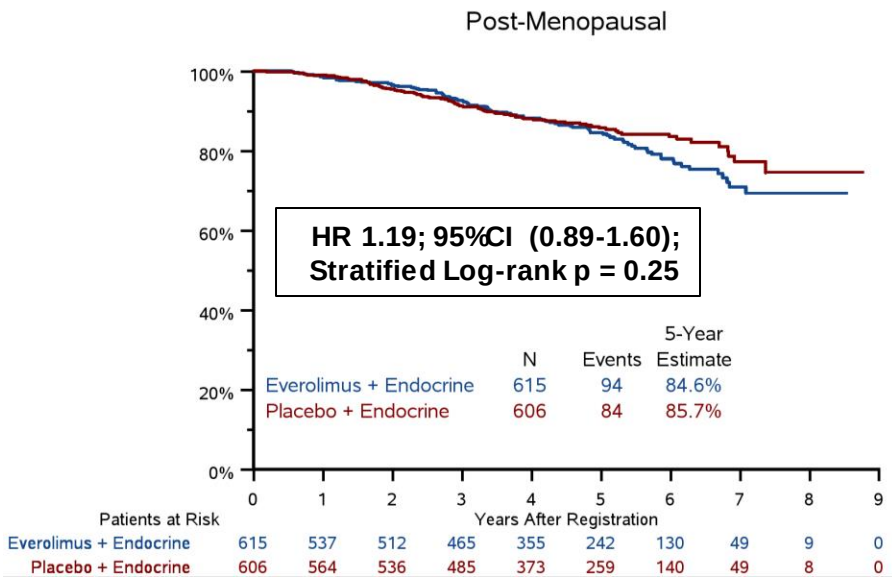
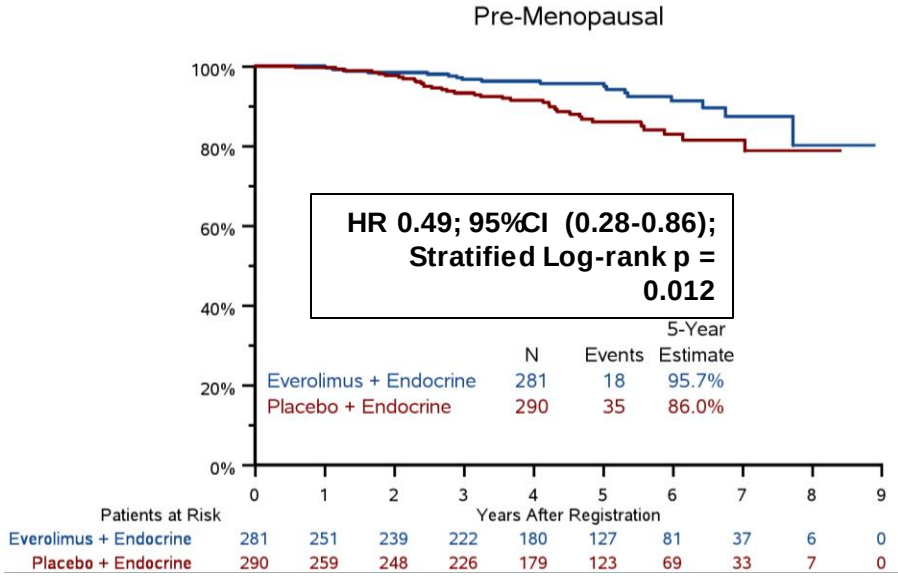
Exploratory Analysis by Menopausal Status-OS





COX REGRESSION MODEL	HR	95% CI	p-value
Treatment arm X Menopausal status Interaction	2.41	1.27-4.57	0.0072

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Secondary Endpoint-Toxicity

Gr 3 + Treatment Related AE

TOXICITY	Everolimus N = 874	Placebo N = 881
Any type	303 (35%)	59 (7%)
Mucositis oral	60 (7%)	2 (0%)
Lymphopenia	36 (4%)	5 (1%)
Hypertriglyceridemia	35 (4%)	3 (0%)
Hyperglycemia	33 (4%)	1 (0%)
Fatigue	22 (3%)	6 (1%)
Neutropenia	22 (3%)	3 (0%)
Leukopenia	20 (2%)	2 (0%)
Hypertension	15 (2%)	6 (1%)
Diarrhea	13 (1%)	3 (0%)
Anemia	10 (1%)	0 (0%)
Hypercholesterolemia	9 (1%)	0 (0%)
Skin infection	8 (1%)	3 (0%)

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Conclusions

Addition of one year of adjuvant everolimus to standard adjuvant ET did not improve IDFS or OS.

We observed low completion rate and increased AEs among patients treated with everolimus.

Among premenopausal patients, the addition of everolimus to ET improved IDFS (HR= 0.64; 95%CI 0.44-0.94; p=0.22) and OS (HR=0.49; 95%CI 0.28-0.86; p=0.012) This observation is hypothesis generating.

San Antonio Breast Cancer Symposium®, December 6-10, 2022

Abemaciclib plus endocrine therapy for HR+, HER2-, node-positive, high-risk early breast cancer: results from a pre-planned monarchE overall survival interim analysis, including 4-year efficacy outcomes

Stephen R.D. Johnston[1], Masakazu Toi, Joyce O'Shaughnessy, Priya Rastogi, Mario Campone, Patrick Neven, Chiun-Sheng Huang, Jens Huober, Georgina Garnica Jaliffe, Irfan Cicin, Sara M. Tolaney, Matthew P. Goetz, Hope S. Rugo, Elzbieta Senkus, Laura Testa, Lucia Del Mastro, Chikako Shimizu, Ran Wei, Ashwin Shahir, Maria Munoz, Belen San Antonio, Valérie André, Nadia Harbeck, Miguel Martin

Overview of monarchE Data Cuts

Current Analysis

Analysis Time points	Interim Analysis[1]	Primary Outcome	Additional Follow-up 1[2] (AFU1)	Overall Survival Interim Analysis (OS IA2)
Date	16 March 2020	08 July 2020	01 April 2021	**01 July 2022**
Median Follow-up (months)	15.5	19.1	27.1	**42.0**
IDFS Events	323	395	565	**835**
Off Study Treatment*	26.4%	41.0%	89.6%	**99.2%**

*0.8% of patients were randomized but never entered treatment period and are not included in these percentages

- OS IA2 was planned to occur 2 years after the primary outcome analysis
- Follow up will continue to final OS analysis

[1]Johnston SRD, et al. J Clin Oncol. 2020;38(34):3987-3998
[2]Harbeck* N, Rastogi* P, et al. Ann Oncol. 2021;32(12):1571-1581
*co-first authors

monarchE Study Design (NCT03155997)

HR+, HER2-, node positive high-risk EBC
- Women or men
- Pre-/postmenopausal
- With or without prior neo- and/or adjuvant chemotherapy
- No metastatic disease
- Maximum of 16 months from surgery to randomization and 12 weeks of ET following the last non-ET

Cohort 1: High risk based on **clinical pathological features**
- ≥4 ALN OR
- 1-3 ALN and at least 1 of the below:
  - Grade 3 disease
  - Tumor size ≥5 cm

Cohort 2: High risk based on **Ki-67**
- 1-3 ALN and
- Ki-67 ≥20% and
- Grade 1-2 and tumor size <5 cm

Stratified for:
- Prior chemotherapy
- Menopausal status
- Region

R 1:1
N = 5637

On-study treatment period
2 years

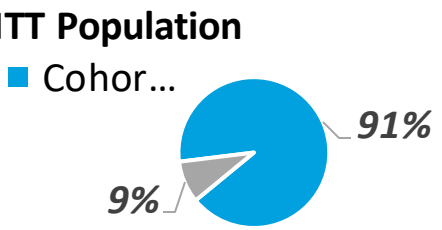
Abemaciclib
(150mg twice daily)
+
Endocrine Therapy: AI or tamoxifen

Endocrine Therapy: AI or tamoxifen

Follow-up period
Endocrine Therapy
3-8 years as clinically indicated

Primary Objective: IDFS
Secondary Objectives: IDFS in high Ki-67 populations, DRFS, OS, Safety, PK, PRO

ITT Population



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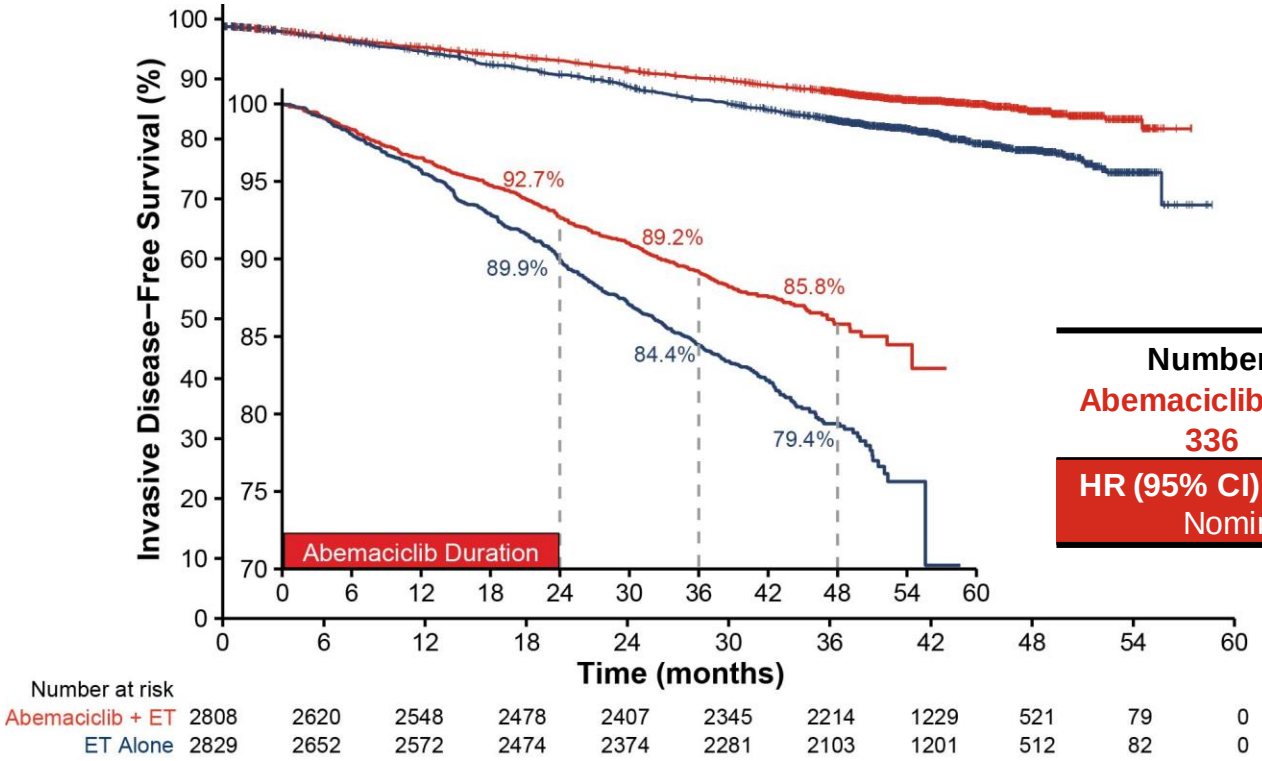
IDFS Benefit in ITT Persists Beyond Completion of Abemaciclib



Number of IDFS events

Abemaciclib + ET	ET Alone
336	499

HR (95% CI): 0.664 (0.578, 0.762)
Nominal $p < 0.0001$

33.6% reduction in the risk of developing an IDFS event with an increase in absolute benefit in IDFS 4-year rates (6.4%) compared to 2-and 3-year IDFS rates (2.8% and 4.8% respectively)

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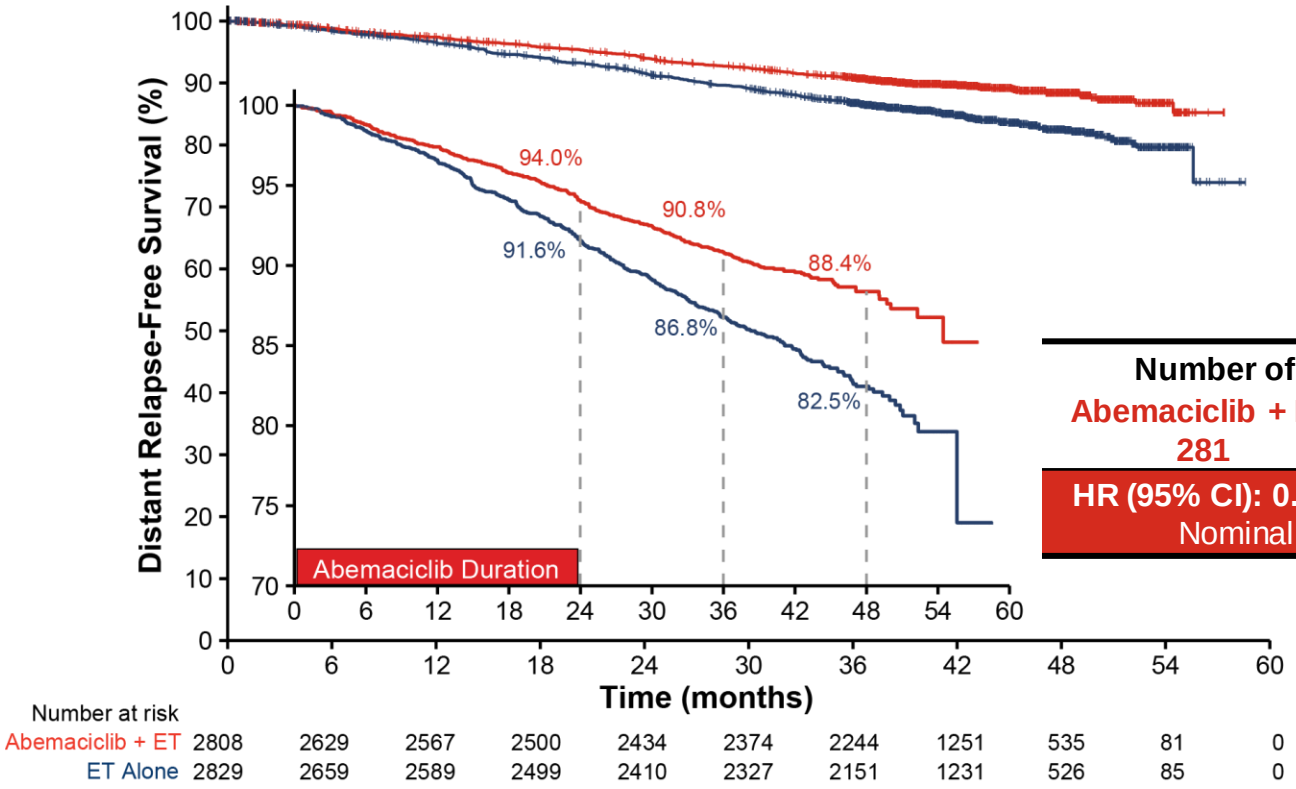
DRFS Benefit in ITT Persists Beyond Completion of Abemaciclib



Number of DRFS events

Abemaciclib + ET	ET Alone
281	421

HR (95% CI): 0.659 (0.567, 0.767)
Nominal p < 0.0001

34.1% reduction in the risk of developing a DRFS event with an increase in absolute benefit in DRFS 4-year rates (5.9%), compared to 2-and 3-year rates (2.5% and 4.1%, respectively)

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Abemaciclib Treatment Benefit Deepened Over Time

Study Treatment Period

Analysis landmark	IDFS	DRFS
	Piecewise HR[a] (95% CI[b])	Piecewise HR[a] (95% CI[b])
Year 0-1	0.782 (0.583, 1.018)	0.725 (0.519, 0.983)
Year 1-2	0.674 (0.521, 0.858)	0.691 (0.521, 0.887)
Year 2-3	0.618 (0.477, 0.788)	0.651 (0.497, 0.851)
Year 3+	0.602 (0.428, 0.803)	0.581 (0.391, 0.818)

[a]Piecewise hazard ratio as a post-hoc analysis was estimated using piecewise exponential model to assess the yearly treatment effect size;
[b]95% credible intervals were calculated by equal tails in the posterior samples of Bayesian exponential models

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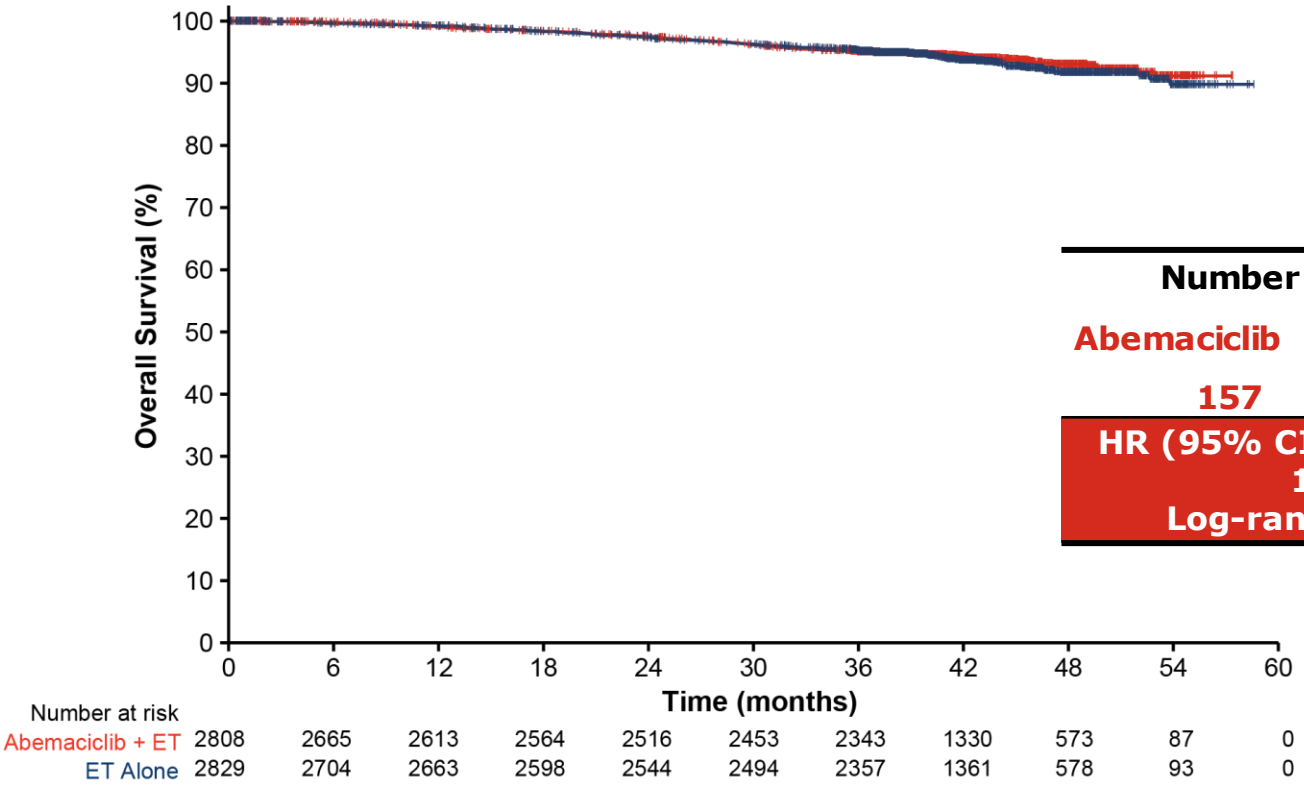
OS Data Remain Immature in ITT



Fewer deaths (157 vs 173) were observed in the abemaciclib plus ET group versus the ET group

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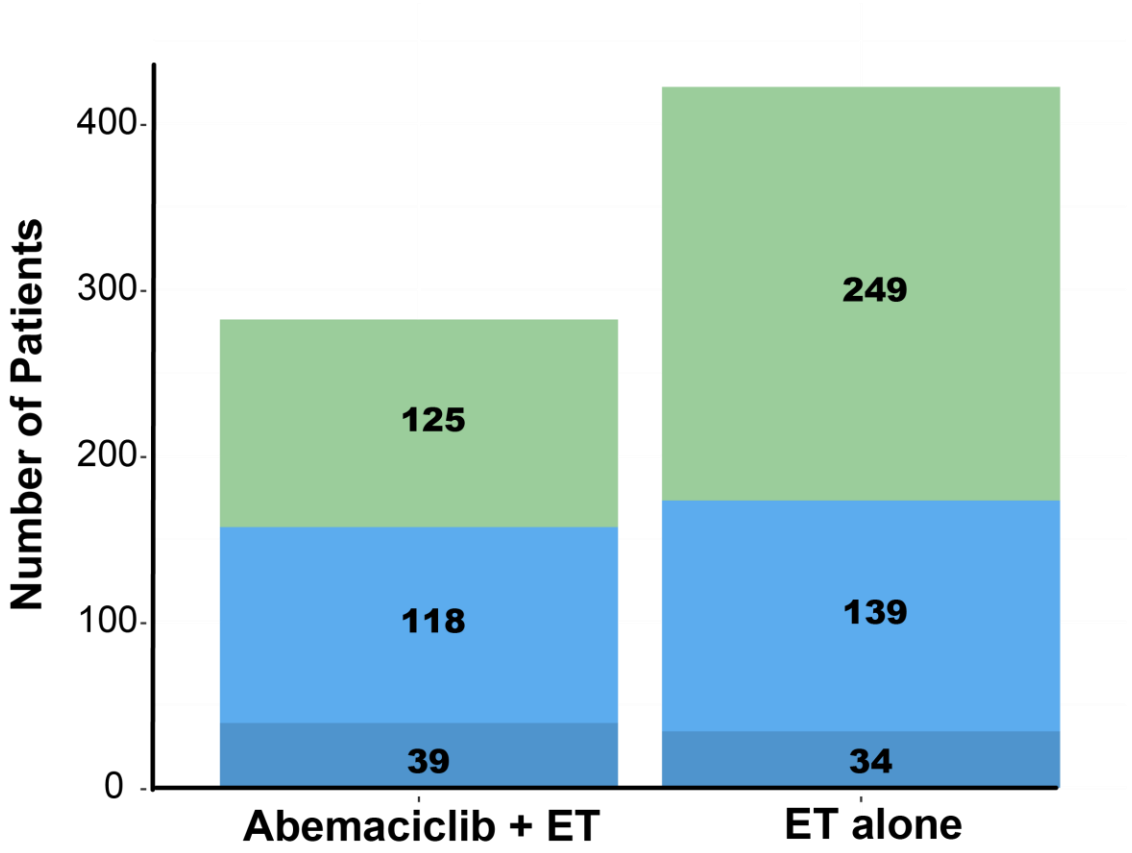
Fewer Patients with Metastatic Disease in the Abemaciclib arm



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Efficacy Outcomes by Cohort

	Cohort 1		Cohort 2	
	Abemaciclib + ET N=2555	ET alone N=2565	Abemaciclib + ET N=253	ET alone N=264
IDFS				
Number of events, n	317	474	19	25
HR (95% CI)	**0.653 (0.567, 0.753)**		**0.773 (0.420, 1.420)**	
Nominal p-value	p<0.0001		p = 0.4048	
4-yr IDFS rate, (95% CI)	85.5 (83.8, 87.0)	78.6 (76.7, 80.4)	NR	NR
DRFS				
Number of events, n	267	402	14	19
HR (95% CI)	**0.652 (0.558, 0.761)**		**0.764 (0.383, 1.526)**	
Nominal p-value	p<0.0001		p = 0.4448	
4-yr DRFS rate, (95% CI)	87.9 (86.4, 89.3)	81.8 (79.9, 83.4)	NR	NR
OS (Immature)				
Number of events, n	147	168	10	5
HR (95% CI)	**0.890 (0.714, 1.111)**		NR	

NR: Not reported. Low event number does not allow reliable statistical analysis.

Cohort 2 enrolled patients with intermediate risk by clinicopathological features. Data remain immature

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Conclusions

- With additional follow-up, the benefit of adjuvant abemaciclib deepened in magnitude with an increase in absolute IDFS and DRFS benefit at 4 years as compared to 2- and 3-year rates
  - Benefit demonstrated across all prespecified subgroups for IDFS and DRFS
- While OS data remain immature at this time, fewer deaths were observed with abemaciclib plus ET group compared to ET alone
  - Continued follow-up is ongoing until final assessment of OS

Primary Results From the Randomized Phase II RIGHT Choice Trial of Premenopausal Patients With Aggressive HR+/HER2– Advanced Breast Cancer Treated With Ribociclib + Endocrine Therapy vs Physician's Choice Combination Chemotherapy

Yen-Shen Lu,[1] Eznal Izwadi Bin Mohd Mahidin,[2] Hamdy Azim,[3] Yesim Eralp,[4] Yoon-Sim Yap,[5] Seock-Ah Im,[6] Julie Rihani,[7] James Bowles,[8] Teresa Delgar Alfaro,[8] Jiwen Wu,[9] Melissa Gao,[8] Khemaies Slimane,[8] Nagi El Saghir[10]

[1]National Taiwan University Hospital, Taipei, Taiwan; [2]Hospital Kuala Lumpur, Kuala Lumpur, Malaysia; [3]School of Medicine, Cairo University, Cairo, Egypt; [4]Acibadem Research Institute of Senology, Acibadem University, Istanbul, Turkey; [5]National Cancer Centre Singapore, Singapore; [6]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; [7]King Hussein Cancer Center, Amman, Jordan; [8]Novartis Pharma AG, Basel, Switzerland; [9]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [10]American University of Beirut Medical Center, Beirut, Lebanon.

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RIGHT Choice study design

- Pre-/perimenopausal women
- HR+/ HER2– ABC (>10% ER+)
- No prior systemic therapy for ABC
- Measurable disease per RECIST 1.1
- Aggressive disease[a]
- Symptomatic visceral metastases
- Rapid disease progression or impending visceral compromise
- Markedly symptomatic non-visceral disease
- ECOG PS ≤ 2[b]
- Total bilirubin ≤ 1.5 ULN
- N = 222[c]

Stratified by (1) the presence or absence of liver metastases and by (2) DFI[d] < or ≥2 years

R 1:1

Ribociclib
(600 mg, 3 weeks on/1 week off)
+
Letrozole or anastrozole + goserelin

Investigators' choice of combination CT[e]

Docetaxel + capecitabine
Paclitaxel + gemcitabine
Capecitabine + vinorelbine

Tumor imaging evaluation
Q6W for 1st 12 weeks, Q8W for next 32 weeks, then Q12W[f]

Primary endpoint
- PFS (locally assessed per RECIST 1.1)

Secondary endpoints
- TTF
- 3-month TFR
- ORR
- CBR
- TTR
- OS
- Safety
- QOL

Exploratory endpoints
- Biomarker analyses
- Healthcare resource utilization

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Baseline characteristics were well balanced

Parameter, n (%)	RIB + ET n = 112	Combo CT n = 110
Median age, years	44.0	43.0
≥40 years	80 (71.4)	72 (65.5)
Race[a]		
Asian	60 (53.6)	58 (52.7)
White	51 (45.5)	52 (47.3)
Histological grade		
Grade 1	10 (8.9)	16 (14.5)
Grade 2	66 (58.9)	61 (55.5)
Grade 3	35 (31.3)	29 (26.4)
≥50% ER+	95 (84.8)	95 (86.4)
PR+	99 (88.4)	102 (92.7)

Parameter, n (%)	RIB + ET n = 112	Combo CT n = 110
Disease status		
De novo	71 (63.4)	73 (66.4)
Visceral metastatic sites[b]		
Liver	56 (50.0)	57 (51.8)
Lung	63 (56.3)	58 (52.7)
Liver or lung	89 (79.5)	85 (77.3)
Aggressive disease characteristic		
Rapid progression	23 (20.5)	18 (16.4)
Symptomatic non-visceral disease	15 (13.4)	16 (14.5)
Symptomatic visceral metastases	74 (66.1)	76 (69.1)
Visceral crisis[c]	61 (54.5)	55 (50.0)

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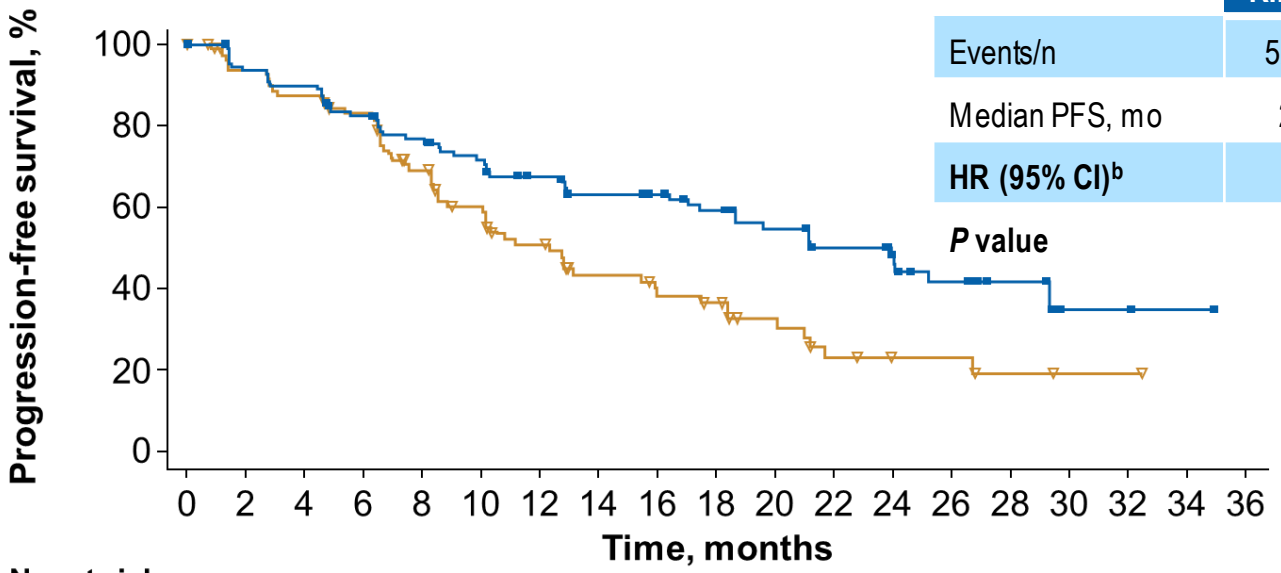
First-line RIB + ET achieved a statistically significant PFS benefit of ≈ 1 year over combination CT in aggressive HR+/HER2− ABC



	RIB + ET	Combo CT
Events/n	52/112	58/110[a]
Median PFS, mo	24.0	12.3
HR (95% CI)[b]	**0.54 (0.36-0.79)**	
***P* value**	**.0007**	

ABC, advanced breast cancer; Combo CT, combination chemotherapy; ET, endocrine therapy; HER2−, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; HR, hazard ratio; IRT, interactive response technology; PFS, progression-free survival; RIB, ribociclib.
[a] Ten patients in CT arm did not receive any treatment; [b] HR is obtained from Cox Proportional-Hazards model stratified by liver metastasis and disease-free interval per IRT.

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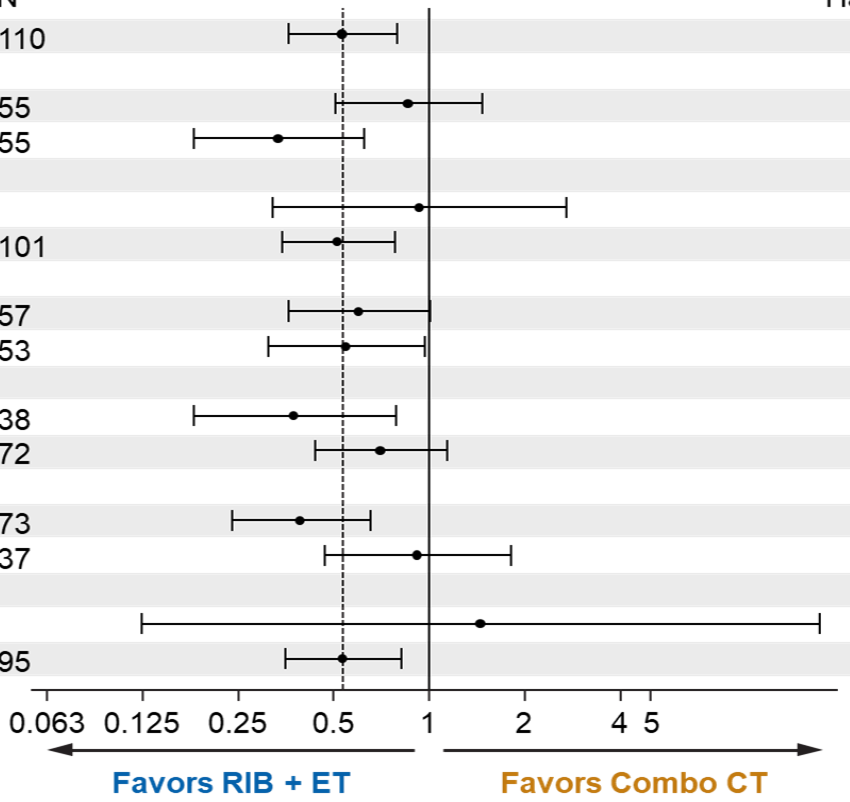
PFS benefit with RIB + ET over combination CT was consistent across most subgroups of patients with aggressive HR+/HER2– ABC

Subgroup	RIB + ET n/N	Combo CT n/N	Hazard Ratio (95% CI)
All patients	52/112	58/110	0.54 (0.36-0.79)
Visceral crisis status			
Yes	33/61	26/55	0.87 (0.51-1.47)
No	19/51	32/55	0.34 (0.18-0.63)
Disease free interval			
<2 years	9/13	6/9	0.94 (0.32-2.73)
≥2 years	43/99	52/101	0.52 (0.34-0.78)
Presence of liver metastasis			
Yes	29/56	31/57	0.60 (0.36-1.01)
No	23/56	27/53	0.55 (0.31-0.97)
Age			
<40 years	12/32	25/38	0.38 (0.18-0.79)
≥40 years	40/80	33/72	0.71 (0.44-1.15)
De novo			
Yes	29/71	42/73	0.40 (0.24-0.66)
No	23/41	16/37	0.92 (0.47-1.82)
Estrogen receptor status			
<50	2/8	3/5	1.46 (0.12-17.08)
≥50	47/95	50/95	0.54 (0.35-0.82)



ABC, advanced breast cancer; Combo CT, combination chemotherapy; ET, endocrine therapy; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; PFS, progression-free survival; RIB, ribociclib.

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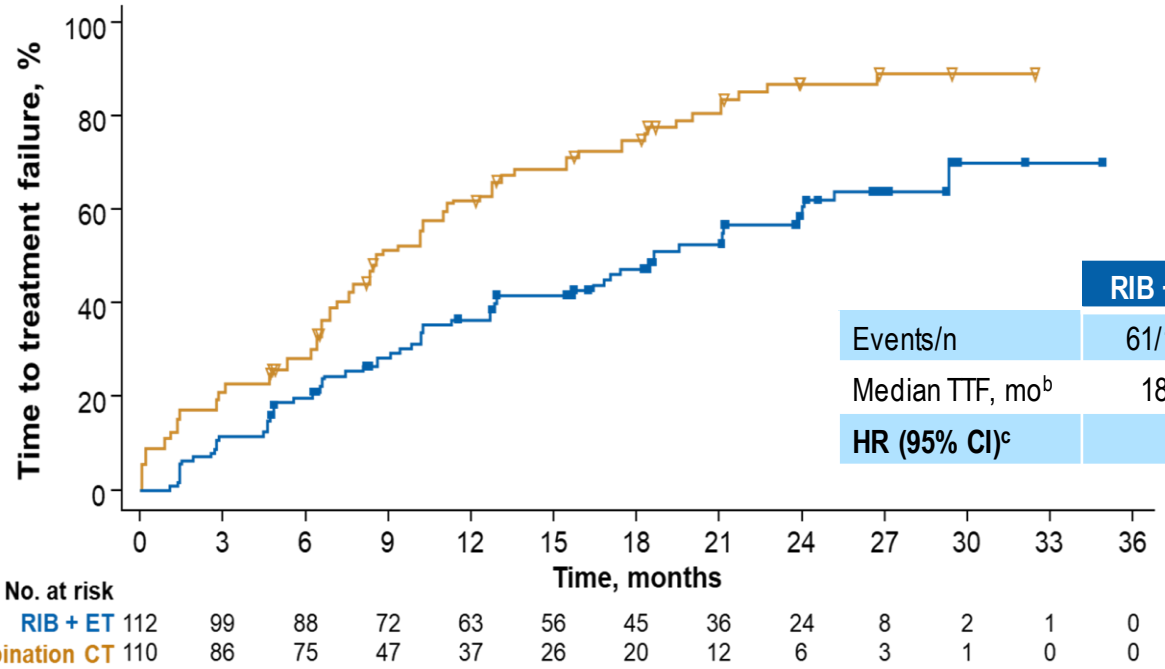
Median time to treatment failure (TTF) was longer with RIB + ET vs combination CT



	RIB + ET	Combo CT
Events/n	61/112	84/110[a]
Median TTF, mo[b]	18.6	8.5
HR (95% CI)[c]	**0.45 (0.32-0.63)**	

- A sensitivity analysis[d] confirmed the TTF findings in the safety set

- The 3-month treatment failure rate[e] in the RIB arm was approximately half (n = 13; 11.6%; 95% CI, 6.3%-19.0%) that in the combination CT arm (n = 24; 21.8%; 95% CI, 14.5%-30.7%)

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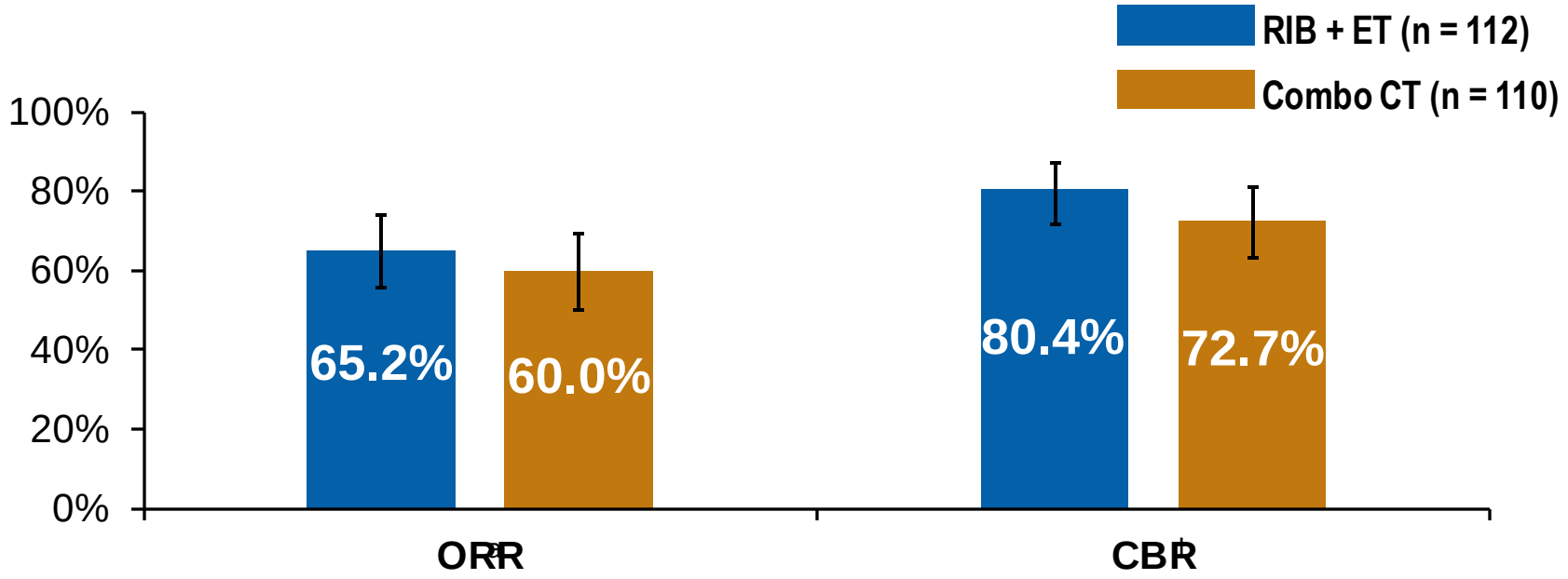
ORR and CBR were similar between RIB + ET and combination CT



- A sensitivity analysis[c] confirmed the ORR and CBR findings in the safety set

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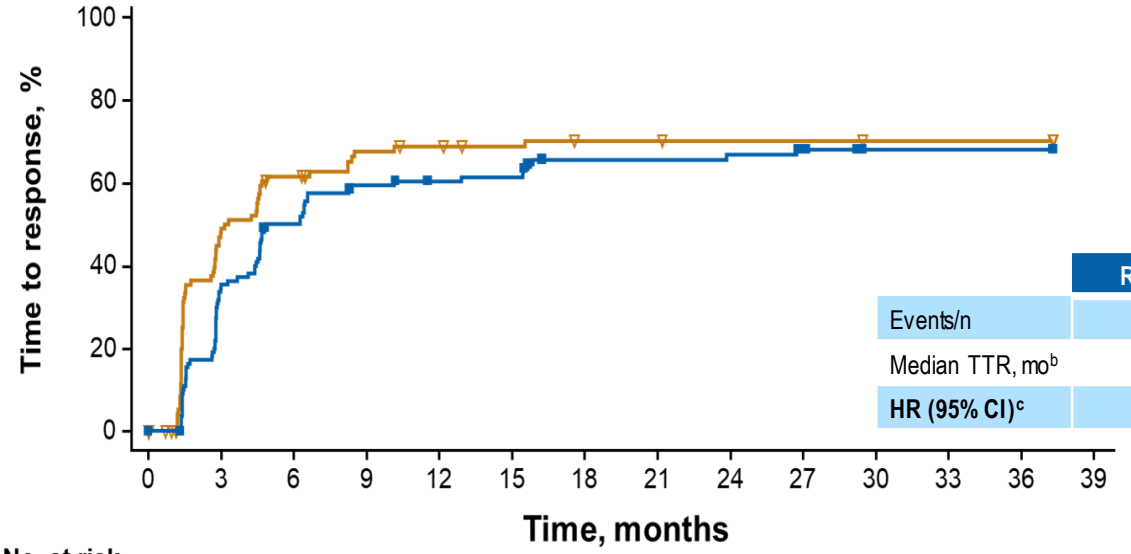
Time to onset of response (TTR) for RIB + ET was similar to combination CT



	RIB + ET	Combo CT
Events/n	73/112	66/110[a]
Median TTR, mo[b]	4.9	3.2
HR (95% CI)[c]	**0.78 (0.56-1.09)**	

A sensitivity analysis[d] confirmed the TTR findings in the safety set

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Fewer dose reductions were observed with RIB + ET vs combination CT

Parameter, n (%)	RIB + ET n = 112	Combo CT n = 100[a]
Number of dose reductions		
0	81 (72.3)	54 (54.0)
1	27 (24.1)	12 (12.0)
2	4 (3.6)	14 (14.0)
≥3	0	20 (20.0)

The median duration of exposure to study treatment was 15.0 months (Q1-Q3, 7.4-24.5 months) in the RIB arm and 8.6 months (Q1-Q3, 6.1-15.0 months) in the combination CT arm[b]

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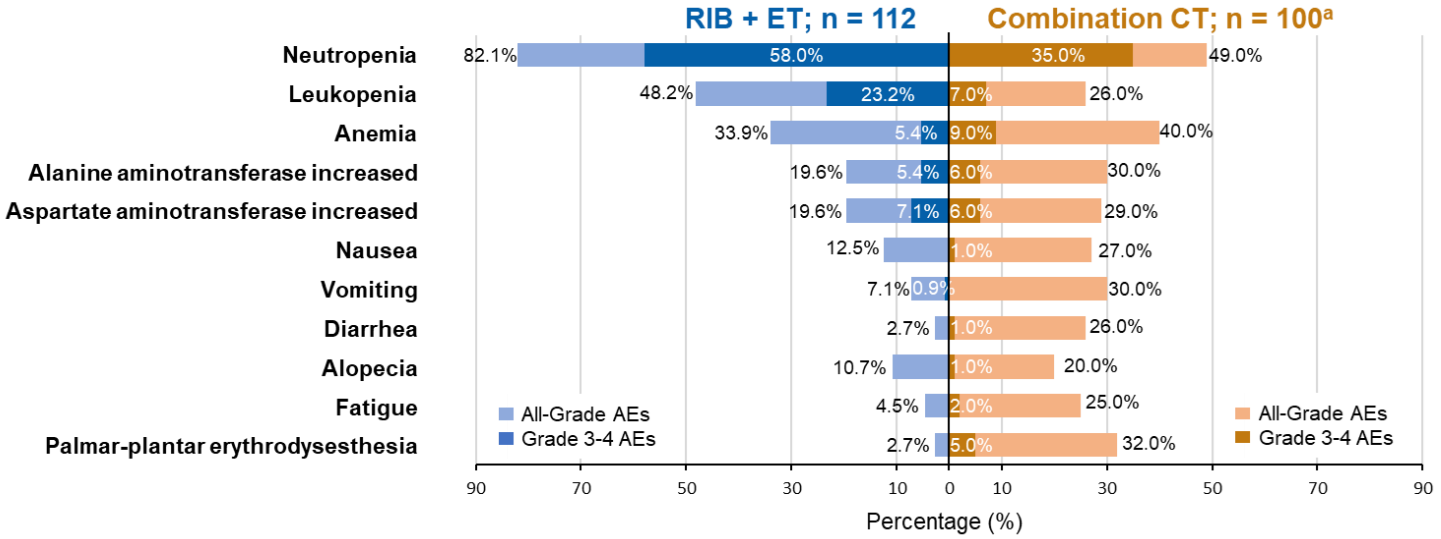
Fewer TRAEs with RIB + ET vs combination CT

n (%)	RIB + ET; n = 112		Combination CT; n = 100[a]	
	All Grade	Grade 3/4	All Grade	Grade 3/4
Total AEs	112 (100.0)	84 (75.0)	100 (100.0)	71 (71.0)
Treatment-related serious AEs	2 (1.8)	1 (0.9)	8 (8.0)	7 (7.0)
Treatment-related AEs leading to discontinuation[b]	8 (7.1)	7 (6.3)	23 (23.0)	7 (7.0)

AEs irrespective of causality (≥20% incidence in either RIB or combination CT arms)



- Two patients (1.8%) in RIB arm[c] and none in CT arm showed grade ≥3 QT prolongation

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Conclusions

- RIGHT Choice is the first prospective study comparing a CDK4/6 inhibitor + ET with combination CT and demonstrating the PFS superiority of RIB + ET over combination CT in patients with HR+/HER2− ABC with aggressive clinical features of rapidly progressing or highly symptomatic disease, including visceral crisis
  - First-line RIB + ET demonstrated a statistically significant PFS benefit (≈1 year longer) vs combination CT (24.0 vs 12.3 months; HR, 0.54) in pre/perimenopausal patients with aggressive HR+/HER2− ABC
- RIB + ET also showed longer TTF than combination CT with similar TTR and ORR between the two treatment groups, matching the high tumor response rate seen with combination CT

PACE: Palbociclib After CDK and Endocrine Therapy A Randomized Phase II Study of Fulvestrant +/- Palbociclib after Progression on CDK4/6 inhibitor for HR+/HER2- Metastatic Breast Cancer

Erica L. Mayer[1]; Yue Ren[1]; Nikhil Wagle[1]; Reshma Mahtani[2]; Cynthia Ma[3]; Angela DeMichele[4]; Massimo Cristofanilli[5]; Jane Meisel[6]; Kathy D Miller[7]; Trevor Jolly[8]; Elizabeth Riley[9]; Rubina Qamar[10]; Priyanka Sharma[11]; Sonya Reid[12]; Natalie Sinclair[1]; Meredith Faggen[1]; Caroline Block[1]; Naomi Ko[13]; Ann Partridge[1]; Wendy Chen[1]; Michelle DeMeo[1]; Victoria Attaya[1]; Amanda Okpoebo[1]; Yuan Liu[14]; Eric Gauthier[14]; Harold J. Burstein[1]; Meredith Regan[1]; Sara M. Tolaney[1]

[1]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; [2]Miami Cancer Institute, Miami, FL; [3]Washington University School of Medicine, St Louis, MO; [4]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; [5]Weill Cornell Medicine, New York, NY; [6]Winship Cancer Institute, Emory University, Atlanta, GA; [7]Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Indianapolis, IN; [8]University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC; [9]University of Louisville Health – Brown Cancer Center, Louisville, KY; [10]Aurora Cancer Care, Milwaukee, WI; [11]University of Kansas Medical Center, Westwood, KS; [12]Vanderbilt-Ingram Cancer Center, Nashville, TN; [13]Boston Medical Center, Boston, MA; [14]Pfizer, Inc, New York, NY.

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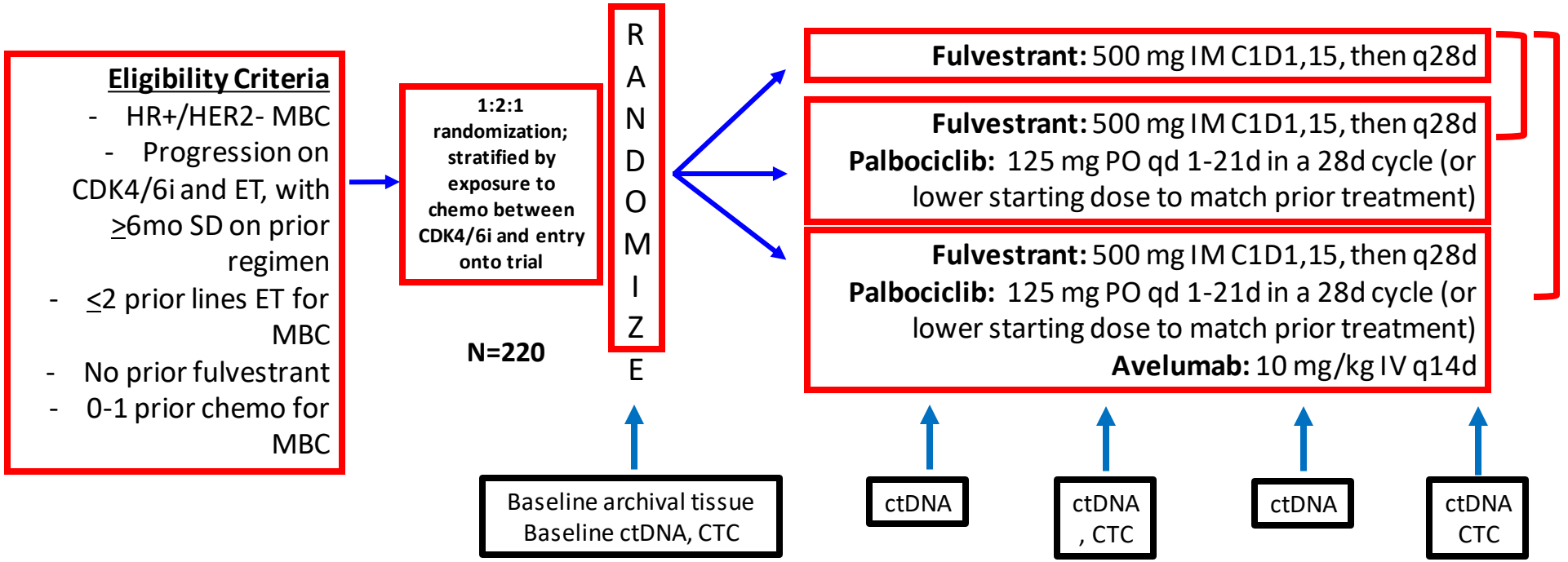
PACE Trial: Schema



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

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

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PACE: Prior Treatment Characteristics

	Fulvestrant (n=55)		Fulvestrant + Palbociclib (N=111)		Fulvestrant + Palbociclib + Avelumab (N=54)		Overall (n = 220)	
	N	%	N	%	N	%	N	%
Prior adjuvant endocrine exposure*	10	**18.2**	32	**28.8**	16	**29.6**	58	**26.4**
Endocrine resistant	45	**81.8**	78	**70.3**	37	**68.5**	160	**72.7**
Endocrine sensitive								
Prior CDK4/6i								
Palbociclib	52	**94.5**	102	**91.9**	46	**85.2**	200	**90.9**
Ribociclib	1	**1.8**	5	**4.5**	4	**7.4**	10	**4.5**
Abemaciclib	2	**3.6**	3	**2.7**	4	**7.4**	9	**4.1**
Duration of prior CDK4/6i + ET								
6-12 months	10	**18.2**	26	**23.4**	16	**29.6**	52	**23.6**
> 12 months	45	**81.8**	84	**75.7**	38	**70.4**	167	**75.9**
Prior chemotherapy for MBC	11	**20.0**	16	**14.4**	9	**16.7**	36	**16.4**
Line of MBC therapy initiated in PACE	3	**5.5**	5	**4.5**	2	**3.7**	10	**4.5**
First line	42	**76.4**	83	**74.8**	44	**81.5**	169	**76.8**
Second Line	10	**18.2**	21	**18.9**	7	**13.0**	38	**17.3**
> Second Line								
Any systemic therapy between prior CDK4/6i and randomization	5	**9.1**	16	**14.4**	5	**9.3**	26	**11.8**

Unknown values are omitted from the table.

*Endocrine resistant: recur <1y of adj ET. Endocrine sensitive: *de novo* MBC, or no adj ET, or recur ≥1y after adj ET. Adapted from ESO-ESMO guidelines, Ann Oncol 2020

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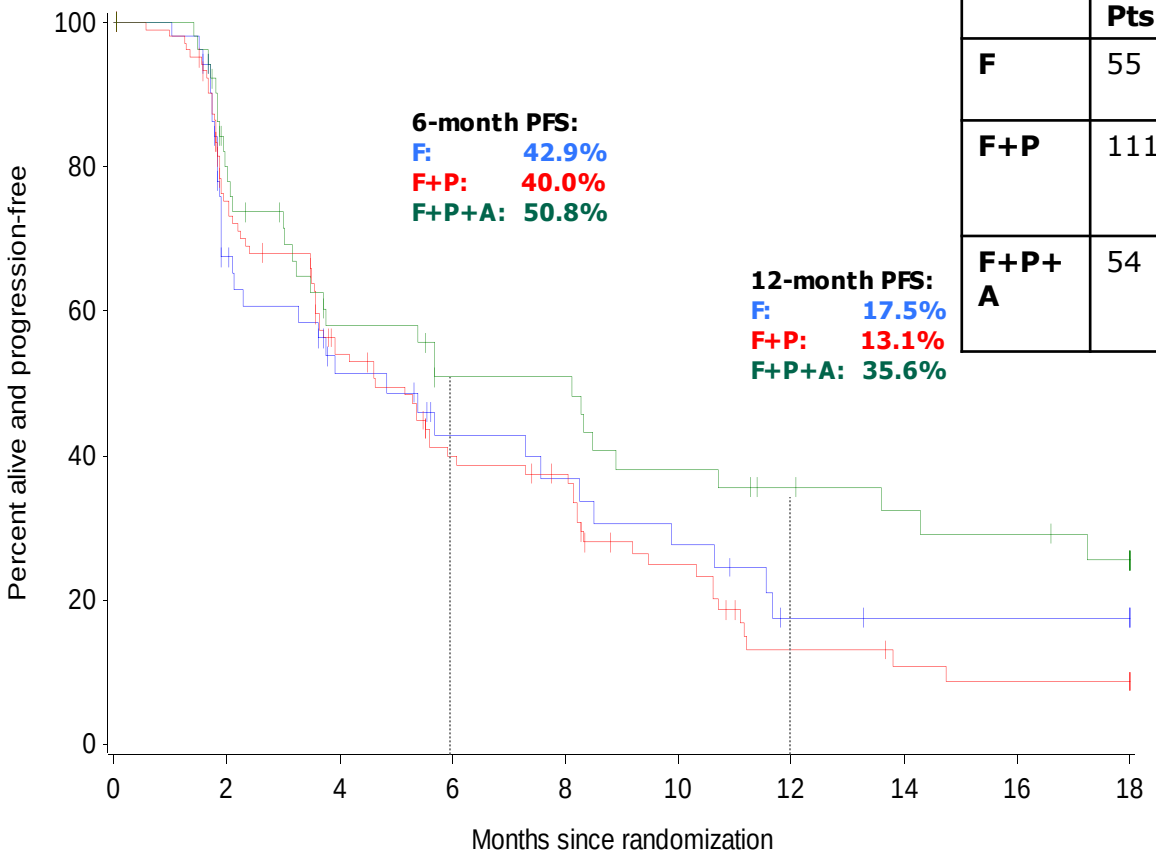
PACE: Progression Free Survival ITT



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

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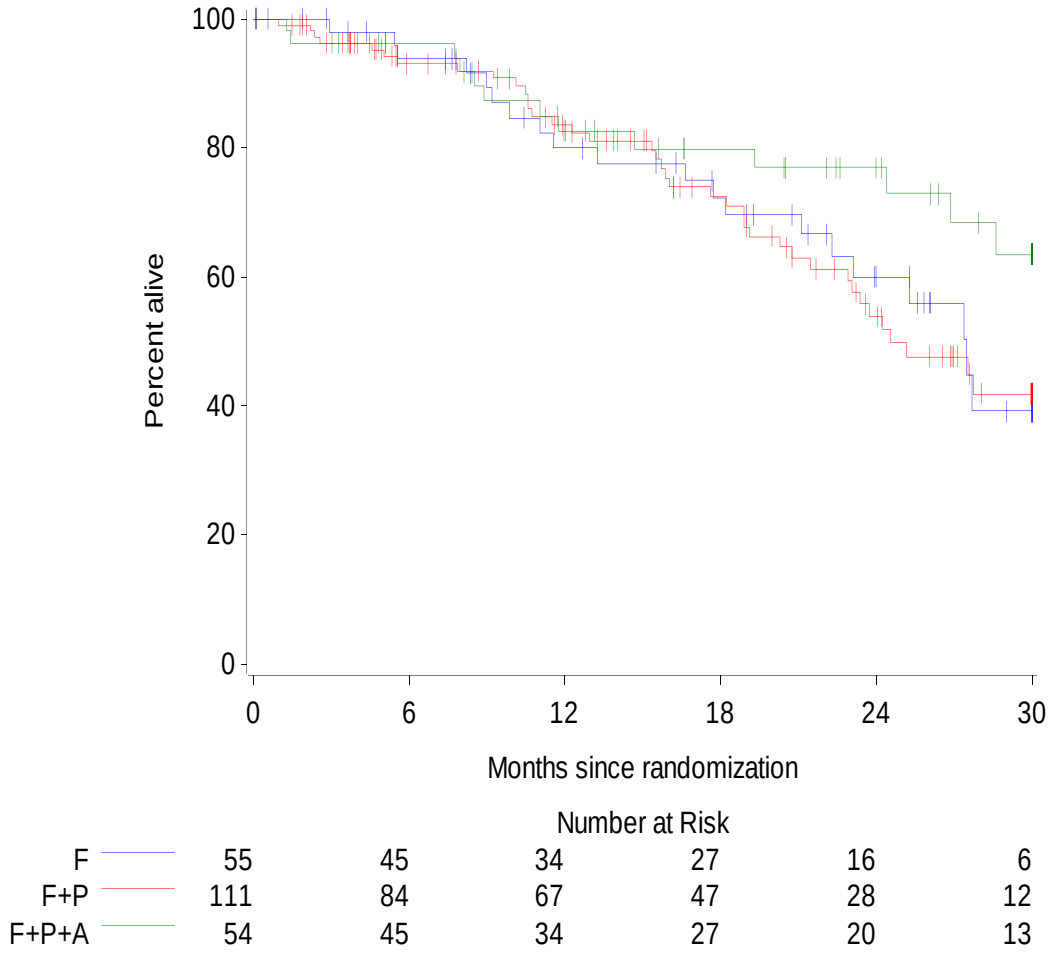
PACE: Overall Survival



	Pts	OS Events	Median OS, mo (90% CI)	HR vs F (90% CI)
F	55	23	**27.5** (21.1, 38.0)	--
F+P	111	43	**24.6** (21.5, 33.3)	1.02 (0.67-1.56)
F+P+A	54	17	**42.5** (26.8, 46.0)	0.68 (0.40-1.15)

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PACE: Treatment Exposure and Toxicity

No dose reductions of fulvestrant or avelumab were permitted.

No patients were reported to have stopped all protocol therapy specifically due to unacceptable treatment-related toxicity.

	Fulvestrant + Palbociclib (N=111)		**Fulvestrant + Palbociclib + Avelumab (N=54)**	
	N	%	N	%
Palbociclib starting dose*				
125 mg qd	68	61.3	28	51.9
100 mg qd	29	26.1	15	27.8
75 mg qd	10	9.0	10	18.5
Palbociclib hold for toxicity	40	36.0	31	57.4
Palbociclib dose reduction	25	22.5	11	20.4
Avelumab hold for toxicity	n/a	n/a	21	38.9

*3 patients did not start protocol therapy

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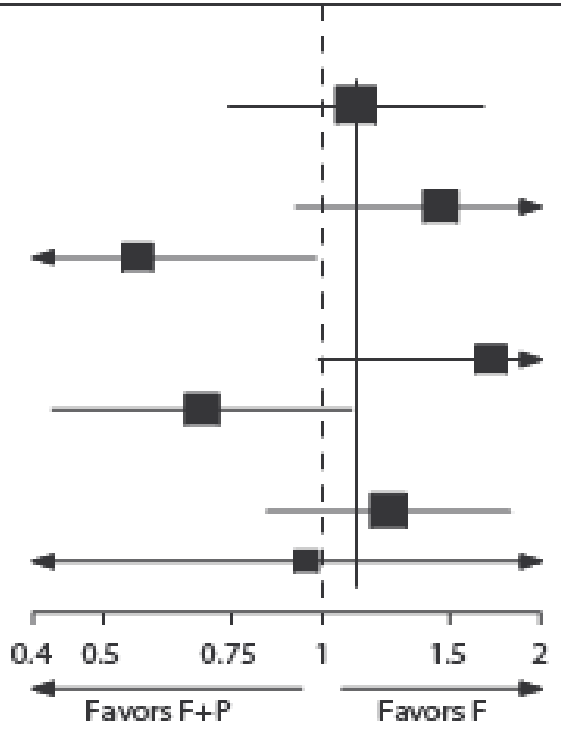
PACE: Exploratory Analysis of Baseline Mutation and Outcome

Subgroup	F+P Events	F+P Patients	F Events	F Patients	Hazard Ratio (90% CI)
Progression-free survival					
All Patients	79	111	34	55	1.11 (0.74-1.66)
Any PIK3CA mutation					
WT	45	63	18	36	1.44 (0.91-2.29)
Mutation	29	39	12	12	0.56 (0.32-0.99)
Any ESR1 mutation					
WT	31	47	13	25	1.70 (0.99-2.95)
Mutation	43	55	17	23	0.68 (0.42-1.09)
Any Rb1 mutation					
WT	67	92	25	42	1.23 (0.83-1.81)
Mutation	7	10	5	6	0.95 (0.36-2.49)



ESR1 mutation 54%, PI3K mutation 35%, Rb 12.5%

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PACE: Conclusions

- Among patients with HR+/HER2- MBC, combining palbociclib with fulvestrant beyond progression on prior CDK4/6i did not significantly improve PFS compared with using fulvestrant alone.
- The observed longer PFS when a PD-L1 inhibitor was added to fulvestrant+palbociclib is an intriguing signal in this HR+ population and deserves further study.
- Baseline ctDNA analyses suggest differential impact of targeted agents based on mutational status.

EMERALD phase 3 trial of elacestrant versus standard of care endocrine therapy in patients with ER+/HER2- metastatic breast cancer: updated results by duration of prior CDK4/6i in metastatic setting

Bardia A,[1*] Bidard FC,[2*] Neven P,[3] Streich G,[4] Montero AJ,[5] Forget F,[6] Mouret-Reynier MA,[7] Sohn JH,[8] Taylor D,[9] Harnden KK,[10] Khong H,[11] Kocsis J,[12] Dalenc F,[13] Dillon P,[14] Babu S,[15] Waters S,[16] Deleu I,[17] Garcia-Saenz J,[18] Bria E,[19] Cazzaniga M,[20] Aftimos P,[21] Cortes J,[22] Tonini G,[23] Tarek Sahmoud,[24] Habboubi N,[24] Grzegorzewski KJ,[24] Kaklamani V[25**]

Oral SERD Trial Landscape in Pretreated mBC

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

1. Bidard FC, et al. *J Clin Oncol.* 2022;40(28):3246-3256. 2. SERENA2. ClinicalTrials.gov identifier: NCT04214288. Accessed November 18, 2022, https://clinicaltrials.gov/ct2/show/NCT04214288; 3. EMBER-3. ClinicalTrials.gov identifier: NCT04975308. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04975308; 4. AMEERA3. ClinicalTrials.gov identifier: NCT04059484. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04059484; 5. Tolaney SM, et al. *Ann Oncol*. 2022; 33(7):S88-S121 (Abstr 212MO); 6. Evaluate Vantage. https://www.evaluate.com/vantage/articles/news/trial-results/roche-has-rare-breast-cancer-setback. Accessed July 20, 2022; 7. acelERA ClinicalTrials.gov identifier: NCT04576455. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04576455; 8. Martin M, et al. *J Clin Oncol*. 2021;39(15):abstr TPS1100; 9. Martin Jimenez M, et al. *Ann Oncol.* 2022;33(7):S88-S121 (abstr 211MO).

EMERALD Phase 3 Study Design

Inclusion Criteria

- Men and postmenopausal women with advanced/metastatic breast cancer
- ER-positive,[a] HER2-negative
- Progressed or relapsed on or after 1 or 2 lines of endocrine therapy for advanced disease, one of which was given in combination with a CDK4/6i
- ≤1 line of chemotherapy for advanced disease
- ECOG PS 0 or 1

R 1:1[b]

- **Elacestrant 400 mg daily[c]**
- **Investigator's choice (SOC):**
  - Fulvestrant
  - Anastrozole
  - Letrozole
  - Exemestane

PD or withdrawal criterion[d]

Follow Up

Two Primary Endpoints:[e]

- PFS in all pts
- PFS in *ESR1*-mut

Stratification Factors:

- *ESR1*-mutation status[f]
- Prior treatment with fulvestrant
- Presence of visceral metastases

All Patients: PFS by Duration of CDK4/6i

Duration on CDK4/6i in the metastatic setting

	At Least 6 Months (87.5%)		At Least 12 Months (66.7%)		At Least 18 Months (46.7%)	
	Elacestrant (n=202)	**SOC Hormonal Therapy (n=205)**	**Elacestrant (n=150)**	**SOC Hormonal Therapy (n=160)**	**Elacestrant (n=98)**	**SOC Hormonal Therapy (n=119)**
Median PFS, months (95% CI)	**2.79** (1.94 - 3.78)	**1.91** (1.87 - 2.14)	**3.78** (2.33 - 6.51)	**1.91** (1.87 - 3.58)	**5.45** (2.33 - 8.61)	**3.29** (1.87 - 3.71)
PFS rate at 6 months, % (95% CI)	34.40 (26.70 - 42.10)	19.88 (12.99 - 26.76)	41.56 (32.30 - 50.81)	21.72 (13.65 - 29.79)	44.72 (33.24 - 56.20)	25.12 (15.13 - 35.10)
PFS rate at 12 months, % (95% CI)	21.00 (13.57 - 28.43)	6.42 (0.75 - 12.09)	25.64 (16.49 - 34.80)	7.38 (0.82 - 13.94)	26.70 (15.61 - 37.80)	8.23 (0.00 - 17.07)
PFS rate at 18 months, % (95% CI)	16.24 (8.75 - 23.74)	3.21 (0.00 - 8.48)	19.34 (9.98 - 28.70)	3.69 (0.00 - 9.77)	21.03 (9.82 - 32.23)	4.11 (0.00 - 11.33)
Hazard ratio (95% CI)	**0.688** (0.535 - 0.884)		**0.613** (0.453 - 0.828)		**0.703** (0.482 - 1.019)	

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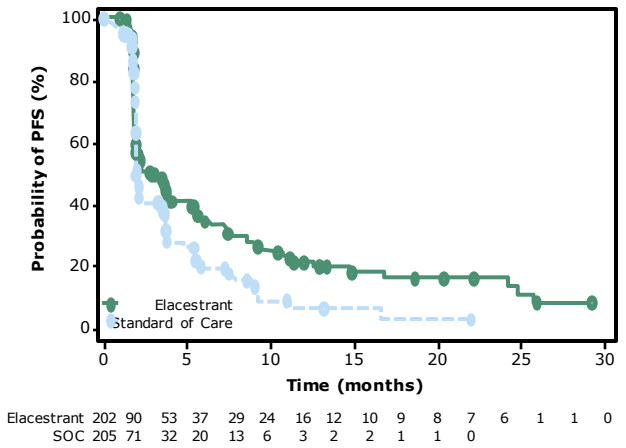
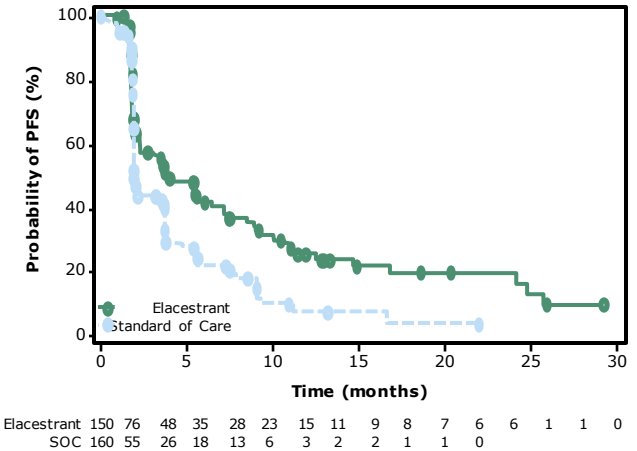
All Patients: PFS by Duration of CDK4/6i

At least 6 mo CDK4/6i



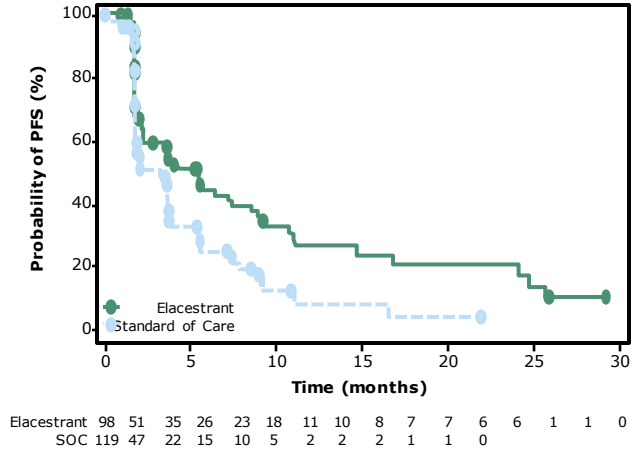
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**2.79** (1.94 - 3.78)	**1.91** (1.87 - 2.14)
PFS rate at 12 months, % (95% CI)	21.00 (13.57 - 28.43)	6.42 (0.75 - 12.09)
Hazard ratio (95% CI)	**0.688** (0.535 - 0.884)	

At least 12 mo CDK4/6i



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

At least 18 mo CDK4/6i



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

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

Duration on CDK4/6i in the metastatic setting

	At Least 6 Months (92.3%)		At Least 12 Months (71.6%)		At Least 18 Months (50.0%)	
	Elacestrant (n=103)	SOC Hormonal Therapy (n=102)	Elacestrant (n=78)	SOC Hormonal Therapy (n=81)	Elacestrant (n=55)	SOC Hormonal Therapy (n=56)
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 6 months, % (95% CI)	42.43 (31.15 - 53.71)	19.15 (9.95 - 28.35)	55.81 (42.69 - 68.94)	22.66 (11.63 - 33.69)	58.57 (43.02 - 74.12)	27.06 (13.05 - 41.07)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
PFS rate at 18 months, % (95% CI)	20.70 (9.77 - 31.63)	0.00 (. - .)	28.49 (14.08 - 42.89)	0.00 (. - .)	30.68 (13.94 - 47.42)	0.00 (. - .)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)		**0.410** (0.262 - 0.634)		**0.466** (0.270 - 0.791)	

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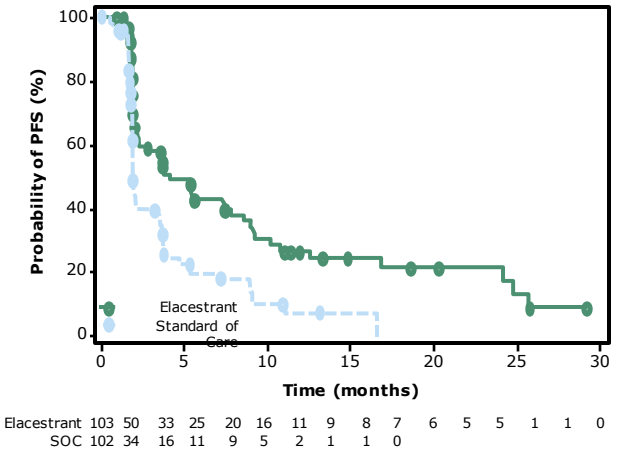
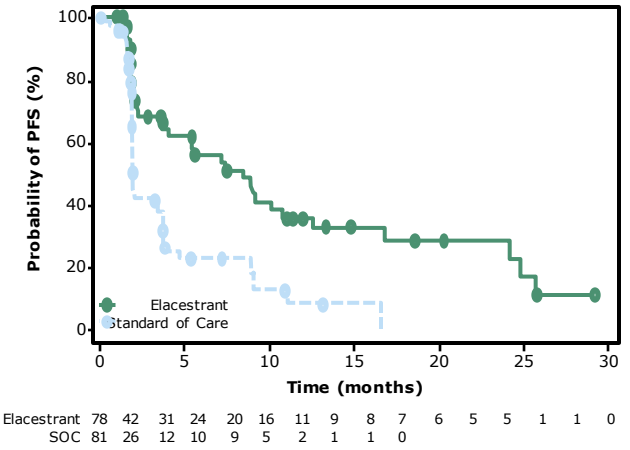
Patients with *ESR1*-mut Tumors: PFS by Duration of CDK4/6i

At least 6 mo CDK4/6i



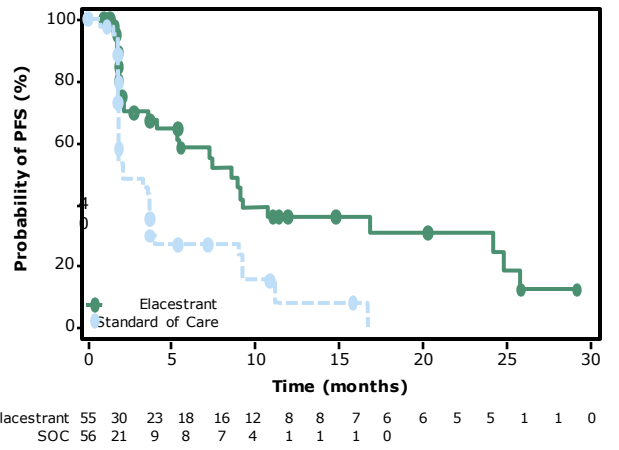
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

At least 12 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)
PFS rate at 12 months, % (95% CI)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)
Hazard ratio (95% CI)	**0.410** (0.262 - 0.634)	

At least 18 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 12 months, % (95% CI)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
Hazard ratio (95% CI)	**0.466** (0.270 - 0.791)	

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Conclusions

EMERALD is the only pivotal trial in 2nd/3rd-line mBC with 100% prior CDK4/6i usage.

Duration of CDK4/6i was associated with PFS in the EMERALD trial. The longer the duration of prior CDK4/6i, the longer PFS on elacestrant as compared with SOC.

This was even more pronounced in patients with *ESR1*-mut tumors, where patients who had at least 12 months of prior CDK4/6i duration achieved a mPFS of 8.6 months with elacestrant vs 2 months mPFS with SOC.

These results showed that elacestrant significantly prolongs PFS vs SOC with a low rate of adverse events.

Elacestrant can become an important oral endocrine monotherapy agent in 2nd/3rd line as an alternative to combination therapies that are associated with challenging safety profiles.

Camizestrant, a next-generation oral SERD *vs* fulvestrant in post-menopausal women with advanced ER-positive HER2-negative breast cancer: Results of the randomized, multi-dose Phase 2 SERENA-2 trial

Mafalda Oliveira, MD, PhD[1], Denys Pominchuk, PhD[2], Zbigniew Nowecki MD[3], Erika Hamilton, MD[4], Yaroslav Kulyaba, MD[5], Timur Andabekov, PhD[6], Yevhen Hotko, MD[7], Tamar Melkadze, MD[8], Gia Nemsadze, MD, PhD[9], Patrick Neven, MD[10], Yuriy Semegen, MD[11], Vladimir Vladimirov, MD[12], Claudio Zamagni, MD[13], Hannelore Denys, MD, PhD[14], Frédéric Forget, MD[15], Zsolt Horvath, MD, PhD[16], Alfiya Nesterova, MD, PhD[17], Maxine Bennett, PhD[18], Bistra Kirova, MBChB, MSc[19], Teresa Klinowska, PhD[20], Justin P O Lindemann, MBChB, MB[18], Delphine Lissa, PharmD, PhD[18], Alastair Mathewson, PhD[18], Christopher J Morrow, PhD[18], Zuzana Traugottova, MD[21], Ruaan van Zyl, PhD[22], Ekaterine Arkania, MD[23]

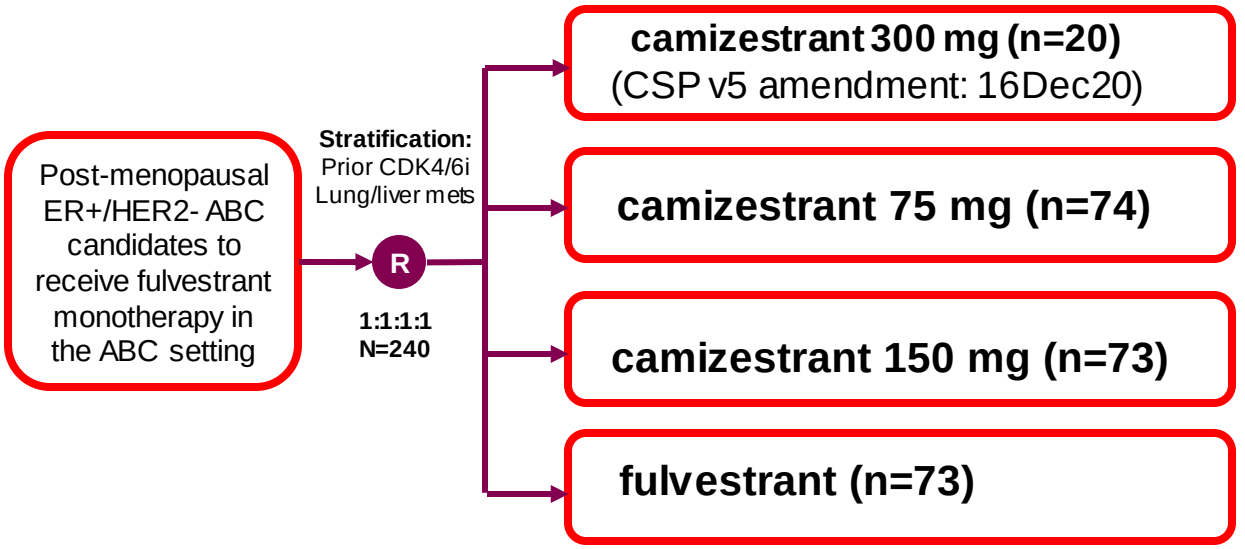
MEDICINE *of* THE HIGHEST ORDER

UNIVERSITY *of* ROCHESTER MEDICAL CENTER

SERENA-2 study overview

Key inclusion/exclusion criteria:

- Recurrence or progression on at least one line of ET
- No prior fulvestrant or oral SERD in ABC
- No more than one line of ET in ABC setting
- No more than one line CT in ABC setting
- Measurable and non-measurable disease



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

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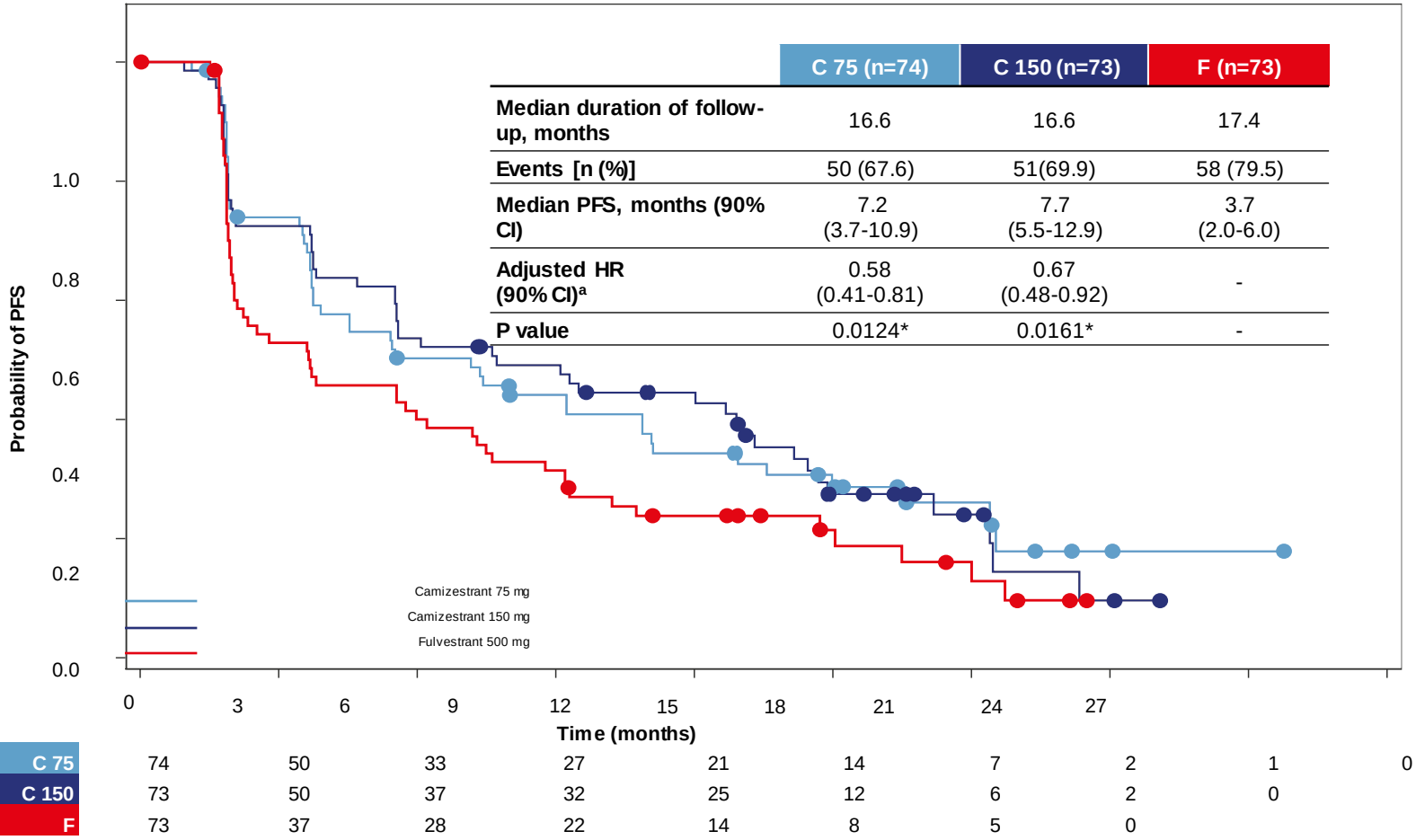
Primary endpoint: PFS by investigator assessment



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

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

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

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

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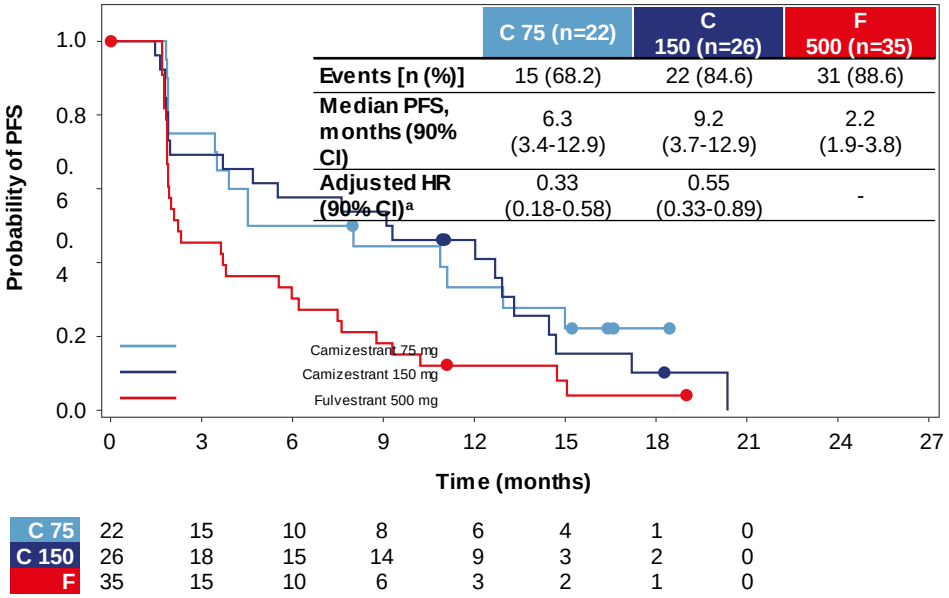
PFS in patients by detectable *ESR1*m

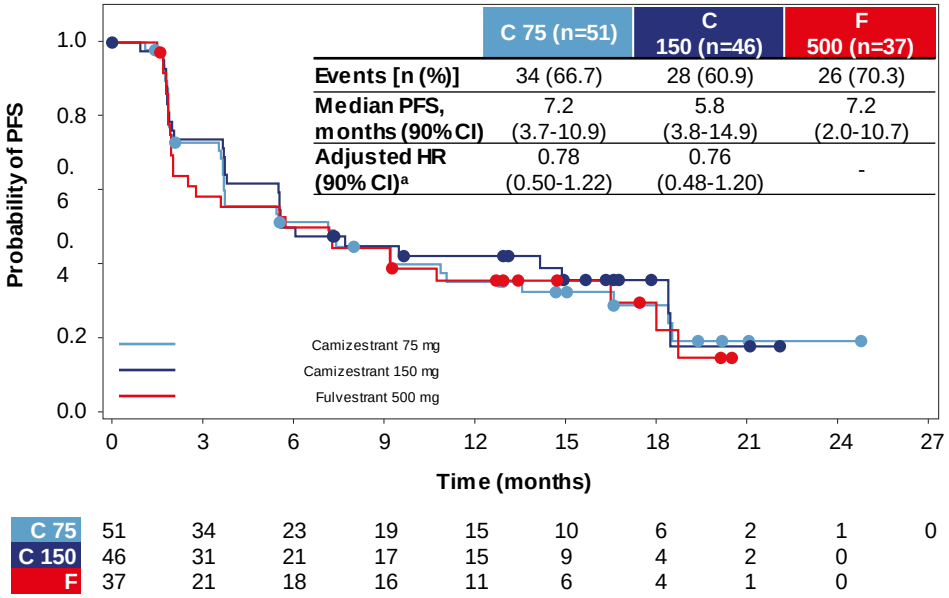
*ESR1*m detectable at baseline



	C 75 (n=22)	C 150 (n=26)	F 500 (n=35)
Events [n (%)]	15 (68.2)	22 (84.6)	31 (88.6)
Median PFS, months (90% CI)	6.3 (3.4-12.9)	9.2 (3.7-12.9)	2.2 (1.9-3.8)
Adjusted HR (90% CI)[a]	0.33 (0.18-0.58)	0.55 (0.33-0.89)	-

C 75	22	15	10	8	6	4	1	0	
C 150	26	18	15	14	9	3	2	0	
F	35	15	10	6	3	2	1	0	

*ESR1*m not detectable at baseline



	C 75 (n=51)	C 150 (n=46)	F 500 (n=37)
Events [n (%)]	34 (66.7)	28 (60.9)	26 (70.3)
Median PFS, months (90% CI)	7.2 (3.7-10.9)	5.8 (3.8-14.9)	7.2 (2.0-10.7)
Adjusted HR (90% CI)[a]	0.78 (0.50-1.22)	0.76 (0.48-1.20)	-

C 75	51	34	23	19	15	10	6	2	1	0
C 150	46	31	21	17	15	9	4	2	0	
F	37	21	18	16	11	6	4	1	0	

- In the sub-population of patients with detectable *ESR1*m at baseline, camizestrant at both doses produces a clinically meaningful improvement in PFS over fulvestrant

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Objective response rate and clinical benefit rate at 24 weeks

Group	n	Number (%) of patients with response	Adjusted response rate (%)	Comparison against fulvestrant		
				Odds ratio	90% CI	2-sided p-value
ORR						
Camizestrant 75 mg	70	11 (15.7)	15.7	1.43	0.63-3.33	0.4789
Camizestrant 150 mg	65	13 (20.0)	20.3	1.96	0.88-4.51	0.1675
Fulvestrant	68	8 (11.8)	11.5			
CBR24						
Camizestrant 75 mg	74	35 (47.3)	48.8	1.48	0.84-2.64	0.2554
Camizestrant 150 mg	73	36 (49.3)	51.0	1.62	0.91-2.89	0.1658
Fulvestrant	73	28 (38.4)	39.1			

The analysis was performed using logistic regression with adjustments for prior use of CDK 4/6 inhibitors and presence of lung and/or liver metastasis.
Includes unconfirmed responses.
Objective response determined for patients with measurable disease only.
Clinical benefit defined as patients with best objective response of complete response or partial response in the first 25 weeks or who have stable disease for at least 23 weeks after randomization.

- Camizestrant at 75 and 150 mg increases both ORR and CBR24 over fulvestrant

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Conclusions

- SERENA-2 met its primary objective: camizestrant at both 75 and 150 mg doses improves PFS over fulvestrant in post-menopausal women with ER+/HER2- ABC
- Camizestrant delivers statistically significant and clinically meaningful PFS benefit at both
  75 and 150 mg doses over fulvestrant in the overall population
- – A clinically meaningful PFS benefit was observed across the pre-specified subgroups of unmet medical need (post-CDK4/6i, lung/liver metastases, *ESR1*m and evidence of ER-driven disease)
- Both camizestrant doses are well tolerated, with infrequent Grade ≥3 TRAEs, dose reductions and discontinuations
- The results of SERENA-2 support the further development of camizestrant in ER+ BC

ARV-471, a PROTAC® estrogen receptor (ER) degrader in advanced ER-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer: phase 2 expansion (VERITAC) of a phase 1/2 study

Sara A Hurvitz,[1] **Anne F Schott**,[2] Cynthia Ma,[3] Erika P Hamilton,[4] Rita Nanda,[5] George Zahrah,[6] Natasha Hunter,[7] Antoinette R Tan,[8] Melinda L Telli,[9] Jesus Anampa Mesias,[10] Rinath Jeselsohn,[11] Pamela Munster,[12] Haolan Lu,[13] Richard Gedrich,[13] Cecile Mather,[13] Janaki Parameswaran,[13] Hyo S Han[14]

[1]UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA; [2]Rogel Cancer Center, University of Michigan Health, Ann Arbor, MI; [3]Washington University, St Louis, MO; [4]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [5]University of Chicago Medicine, Chicago, IL; [6]Norwalk Hospital, Norwalk, CT; [7]Seattle Cancer Care Alliance, Seattle, WA; [8]Levine Cancer Institute, Atrium Health, Charlotte, NC; [9]Stanford University School of Medicine, Stanford, CA; [10]Albert Einstein College of Medicine, Bronx, NY; [11]Dana-Farber Cancer Institute, Boston, MA; [12]University of California San Francisco, San Francisco, CA; [13]Arvinas Operations, Inc, New Haven, CT; [14]Moffitt Cancer Center, Tampa, FL

Background

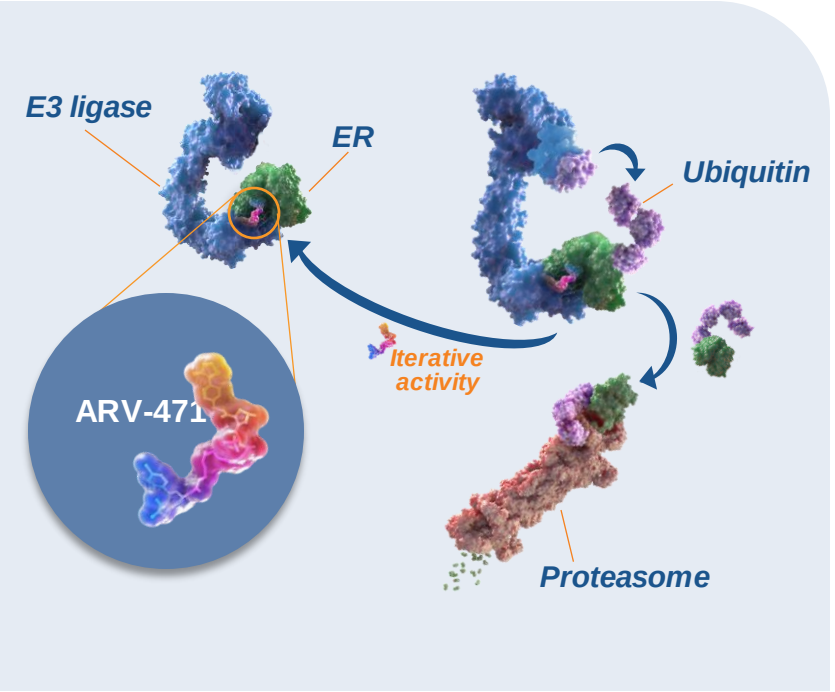
ARV-471 is a selective, orally administered PROTAC® protein degrader that targets wild-type and mutant ER[1]

ARV-471 directly binds an E3 ubiquitin ligase and ER to trigger ubiquitination of ER and its subsequent proteasomal degradation

- In contrast, SERDs indirectly recruit the ubiquitin-proteasome system, secondary to conformational changes and/or immobilization of ER[2]

Limitations of the SERD fulvestrant include its intramuscular route of administration[3] and only 40%–50% ER protein degradation at its optimal dose[4,5]

ARV-471 treatment yielded substantially greater ER degradation and tumor growth inhibition than fulvestrant in breast cancer xenograft models[1]



Phase 1/2 Study Design[a]

First-in-human, open-label, 3-part study of ARV-471 alone or in combination with palbociclib in patients with ER+/HER2- locally advanced/metastatic breast cancer

Phase 1 dose escalation (Part A)	Phase 2 cohort expansion (Part B; VERITAC)	Phase 1b combination (Part C)
Treatment ARV-471 orally	**Treatment** ARV-471 orally	**Treatment** ARV-471 plus palbociclib orally
Primary objective • Evaluate the safety and tolerability of ARV-471 in order to estimate the MTD and select the RP2Ds	**Primary objective** • Assess the antitumor activity of ARV-471	**Primary objective** • Evaluate the safety and tolerability of ARV-471 plus palbociclib and select the RP2D of the combination

[a]ClinicalTrials.gov: NCT04072952

ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; MTD=maximum tolerated dose; RP2D=recommended phase 2 dose

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TRAEs Reported in ≥10% of Patients Overall (VERITAC)

	200 mg QD (n=35)			500 mg QD (n=36)			Total (N=71)		
n (%)	Grade 1	Grade 2	Grade 3/4[a]	Grade 1	Grade 2	Grade 3/4[b]	Grade 1	Grade 2	Grade 3/4
Any TRAE	13 (37)	13 (37)	2 (6)	11 (31)	9 (25)	3 (8)	24 (34)	22 (31)	5 (7)
Fatigue	8 (23)	6 (17)	0	7 (19)	2 (6)	1 (3)	15 (21)	8 (11)	1 (1)
Nausea	2 (6)	3 (9)	0	6 (17)	1 (3)	0	8 (11)	4 (6)	0
Arthralgia	4 (11)	0	0	5 (14)	0	0	9 (13)	0	0
Hot flush	6 (17)	0	0	1 (3)	0	0	7 (10)	0	0
AST increased	3 (9)	1 (3)	0	2 (6)	1 (3)	0	5 (7)	2 (3)	0

[a]Grade 3/4 TRAEs in the 200-mg QD cohort were grade 3 QT prolonged (n=1; same TEAE that led to discontinuation as shown in the prior slide) and grade 3 thrombocytopenia and grade 4 hyperbilirubinemia (n=1)
[b]Grade 3/4 TRAEs in the 500-mg QD cohort were grade 3 fatigue, decreased appetite, and neutropenia (n=1 each)
AST=aspartate aminotransferase; QD=once daily; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event

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Primary Endpoint: Clinical Benefit Rate[a] (VERITAC)

	200 mg QD (n=35)	500 mg QD (n=36)	Total (N=71)
CBR, % (95% CI)	37.1 (21.5–55.1)	38.9 (23.1–56.5)	38.0 (26.8–50.3)
Patients with mutant ESR1	(n=19)	(n=22)	(n=41)
CBR, % (95% CI)	47.4 (24.4–71.1)	54.5 (32.2–75.6)	51.2 (35.1–67.1)

[a]Rate of confirmed complete response or partial response or stable disease ≥24 weeks
CBR=clinical benefit rate; *ESR1*=estrogen receptor 1 gene; QD=once daily

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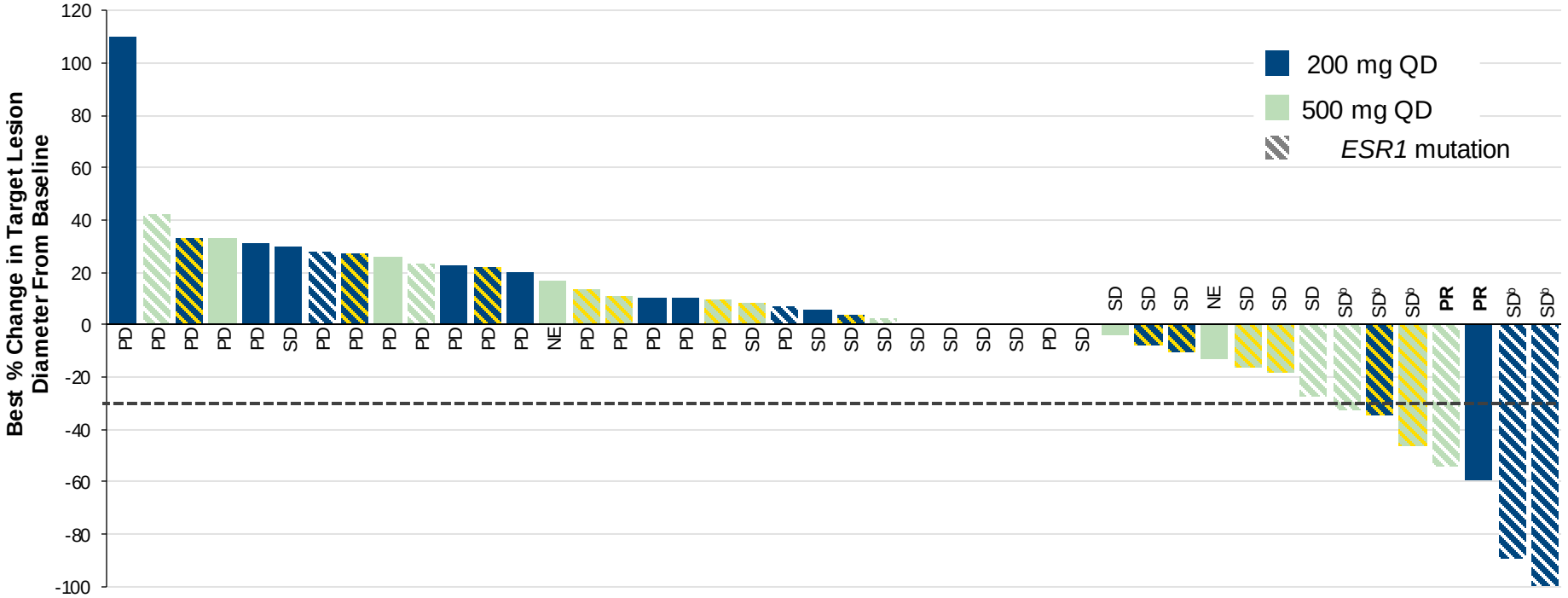
Tumor Response[a] (VERITAC)



[a]Includes patients with measurable disease (n=44); 1 patient with measurable disease at baseline and PD as best overall response was excluded due to lack of complete set of target lesion measurements on-study

[b]Patient had an unconfirmed partial response

ESR1=estrogen receptor 1 gene; NE=not evaluable due to missing data for best overall response; PD=progressive disease; PR=confirmed partial response; QD=once daily; SD=stable disease

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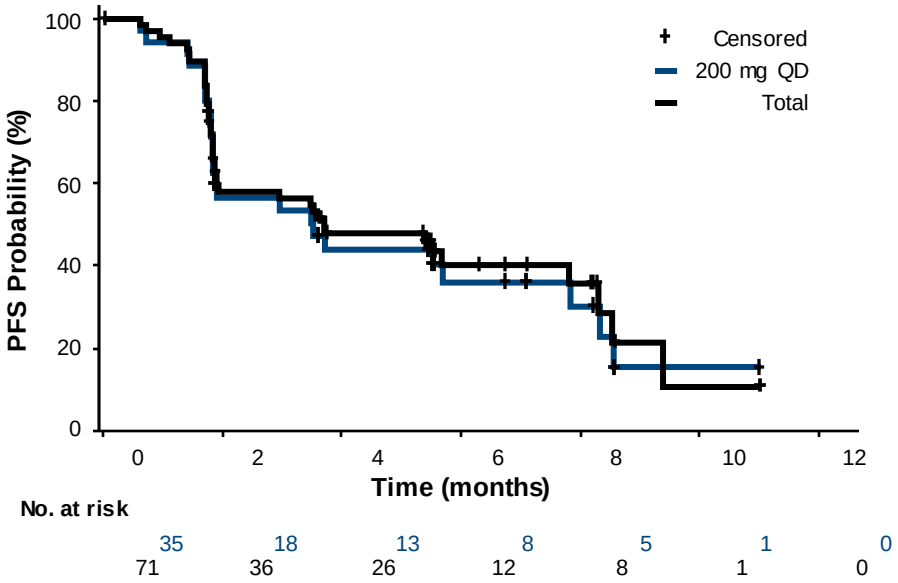
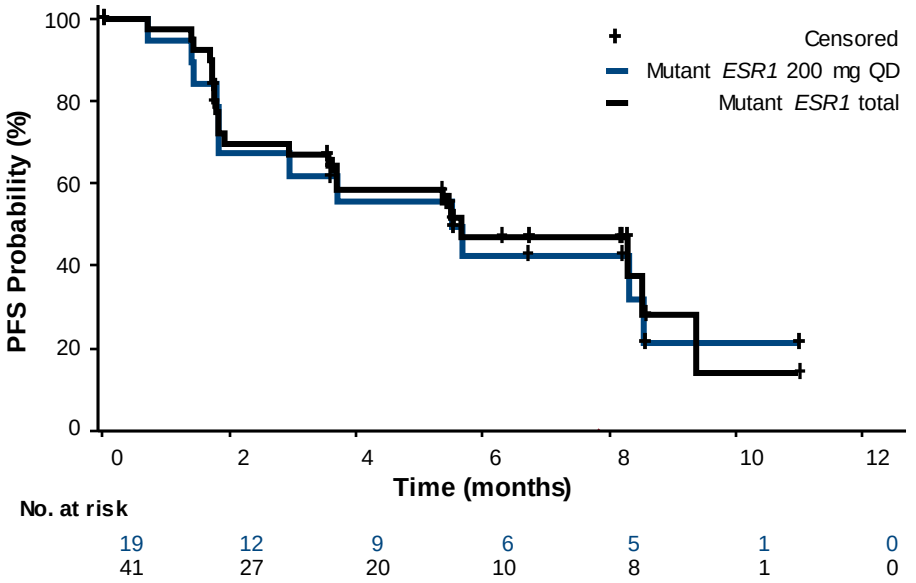
Progression-Free Survival[a] (VERITAC)

	All Patients	
	200 mg QD (n=35)	Total (N=71)
Events, n (%)	24 (68.6)	41 (57.7)
mPFS, mo (95% CI)	3.5 (1.8–7.8)	3.7 (1.9–8.3)



	Mutant *ESR1*	
	200 mg QD (n=19)	Total (n=41)
Events, n (%)	12 (63.2)	22 (53.7)
mPFS, mo (95% CI)	5.5 (1.8–8.5)	5.7 (3.6–9.4)



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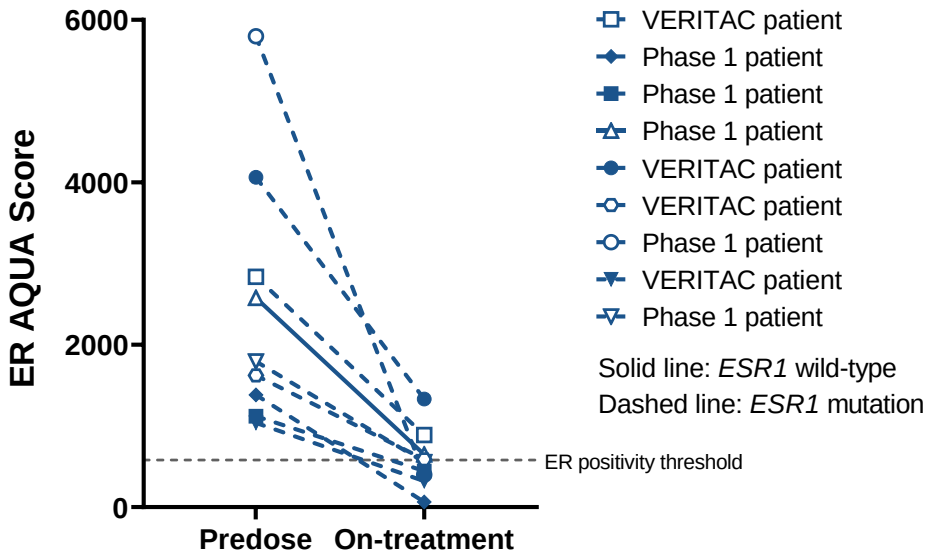
ER Degradation[a] With 200 mg QD ARV-471 (Phase 1/VERITAC)



Median ER degradation was 69% (range: 28%–95%)

Mean ER degradation was 71%

[a]ER immunoreactivity analyzed by QIF using the AQUA method, and ER positivity threshold derived by examining AQUA scores and visually inspecting all samples in the dataset to determine a cut point for ER positivity; *ESR1* mutation status determined from tumor biopsy (n=1) or circulating tumor DNA (n=8)
AQUA=automated quantitative analysis; ER=estrogen receptor; *ESR1*=estrogen receptor 1 gene; QD=once daily; QIF=quantitative immunofluorescence

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Conclusions

- ARV-471 showed clinical activity in the VERITAC expansion cohorts of heavily pretreated patients (4 median prior regimens, 100% with prior CDK4/6 inhibitors, and 79% with prior fulvestrant) with ER+/HER2- advanced breast cancer
  - CBR was 37.1% and 38.9% in the 200- and 500-mg QD cohorts, respectively
  - Clinical benefit was also observed in the *ESR1* mutation subgroup (CBR of 47.4% and 54.5% in the 200- and 500-mg QD cohorts, respectively)
- ARV-471 had a manageable AE profile; most AEs were grade 1/2
- ARV-471 200 mg QD was selected as the phase 3 monotherapy dose based on comparable efficacy, favorable tolerability, and robust ER degradation

AE=adverse event; CBR=clinical benefit rate; CDK=cyclin-dependent kinase; ER=estrogen receptor; *ESR1*=estrogen receptor 1 gene; HER2=human epidermal growth factor receptor 2; QD=once daily

Practice changing?

- Confirmatory:
  - MonarchE with longer follow-up
  - CDK 4/6 inhibition in visceral disease/crisis
- Intriguing
  - Elacestrant benefit in patients with longer CDK 4/6 inhibitor exposure
- Disappointing (but not really surprising)
  - Palbociclib through progression (trial design different from MAINTAIN)
  - Adjuvant everolimus

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