THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

PRIMO 2025, Practical Recommendations in Immunotherapy & Molecular Oncology Meeting
Honolulu, HI.

Major Endocrine and Targeted Therapy Advances In the Treatment of HR+/HER2- Breast Cancer

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Breast Cancer 2025

- *Breast cancer is one of the most common cancers with greater than 1,500,000 cases and 500,000 deaths each year worldwide.*

- *Clinically this heterogeneous disease is categorized into several subtypes: ER+/PR+/- HER2-/low, HER2+ER+/-, TNBC HER2-/low. ER+, HER2 low or negative is the most sub-type.*

- *Metastatic Breast Cancer: Goals of Therapy*
  - *Decrease tumor burden*
  - *Improve progression free survival (PFS)*
  - *Alleviate symptoms*
  - *Maintain or improve quality of life (QOL)*
  - ***Improve overall survival (OS)***

Targeted Therapy, Cell Cycle Control, in Metastatic Breast Cancer

A new standard of care in first- and second-line in 2025

Results of Pivotal CDK 4/6 Inhibitor Trials

Trial	CDK Inhibitor	Line of Therapy (Endocrine Rx)	Menopausal Status	PFS HR	Statistical Significance	OS HR	Statistical Significance
PALOMA-2	Palbociclib	1st Line/AI	Post	0.56	Yes	0.96	No
MONALEESA-2	Ribociclib	1st Line/AI	Post	0.57	Yes	**0.76**	**Yes**
MONALEESA-7*	Ribociclib	1st Line/AI or Tam	Pre/Peri	0.55	Yes	**0.70**	**Yes**
MONARCH-3	Abemaciclib	1st Line/AI	Post	0.54	Yes	0.80	No
PALOMA-3	Palbociclib	2nd Line/Fulv	Pre/Post	0.46	Yes	0.81	No
MONARCH-2	Abemaciclib	2nd Line/Fulv	Pre/Post	0.55	Yes	**0.78**	**Yes**
MONALEESA-3	Ribociclib	1st /2nd Line/Fulv	Pre/Post	0.59	Yes	**0.72**	**Yes**

**PFS/OS data reported for approved AI subset. Abbreviations: CDK=Cyclin-dependent kinase; Rx=therapy; PFS=progression-free survival; HR=hazard ratio; OS=overall survival; AI=aromatase inhibitor; Fulv=fulvestrant; NR=not reported*

References:

i. *PALOMA-2: Finn R et. al. N Engl J Med. 2016; Rugo HS et al. Breast Cancer Res Treat. 2019; Finn R et. al. ASCO 2022.*
ii. *MONALEESA-2: Hortobagyi G et al. N Engl J Med. 2016; Hortobagyi G et al. Ann Oncol. 2018; Hortobagyi G et al. N Engl J Med. 2022.*
iii. *MONALEESA-7: Tripathy D et al. Ann Oncol. 2018; Im S-A et al. N Engl J Med. 2019. [Note PFS/OS data reported for approved AI subset].*
iv. *MONARCH-3: Goetz M et al. J Clin Oncol. 2017; Johnson S et al. npj Breast Cancer. 2019; Goetz M et al. SABCS 2023.*
v. *PALOMA-3: Turner N et al. N Engl J Med. 2015; Cristofanilli M et al. Lancet Oncol. 2016; Turner N et al. N Engl J Med. 2018.*
vi. *MONARCH-2: Sledge G et al. J Clin Oncol. Sledge G et al. JAMA Oncol. 2019.*
vii. *MONALEESA-3: Slamon D et al. J Clin Oncol. 2018; Slamon D et al. N Engl J Med. 2020.*

The NEW ENGLAND JOURNAL of MEDICINE

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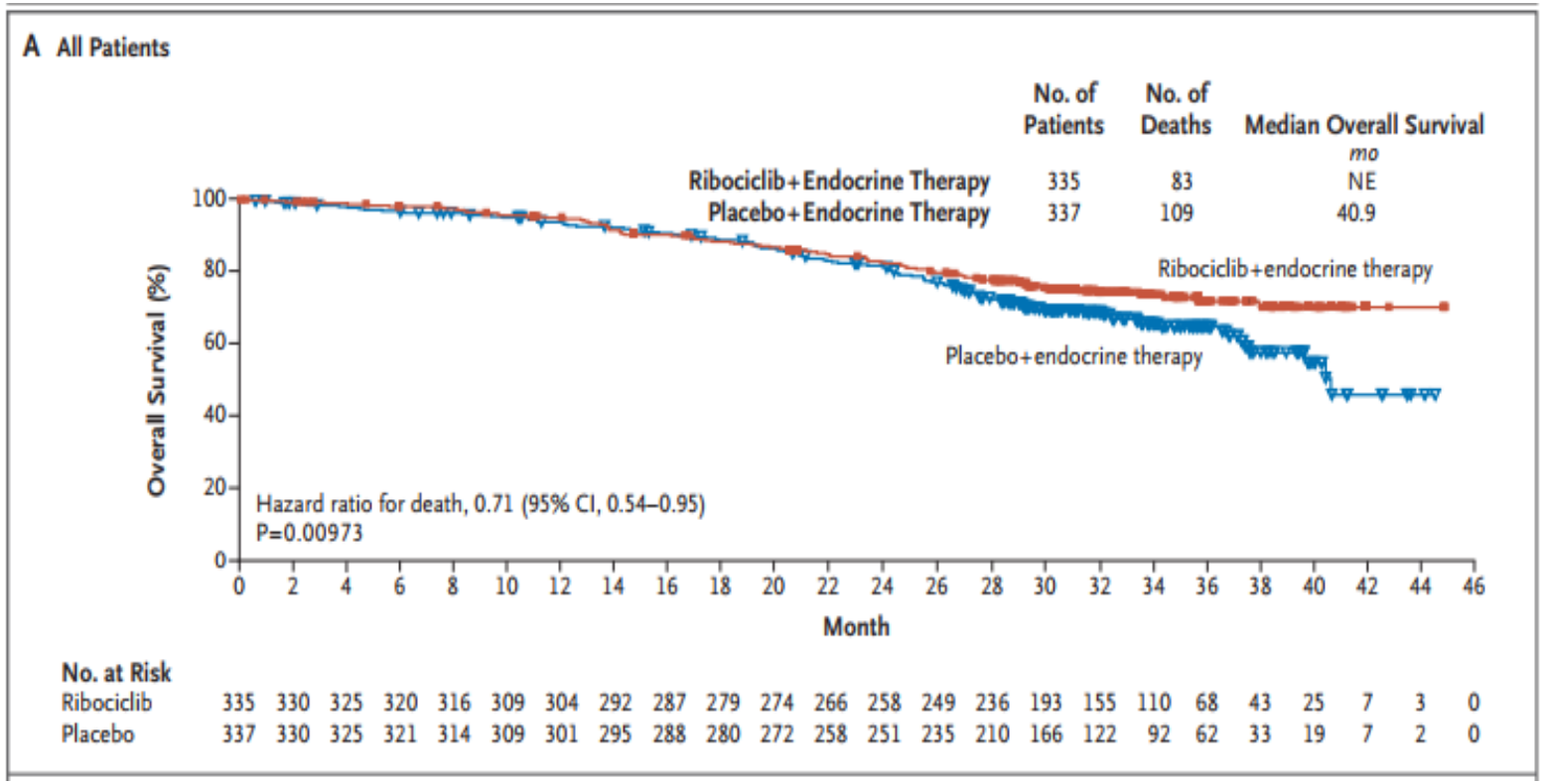
Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer

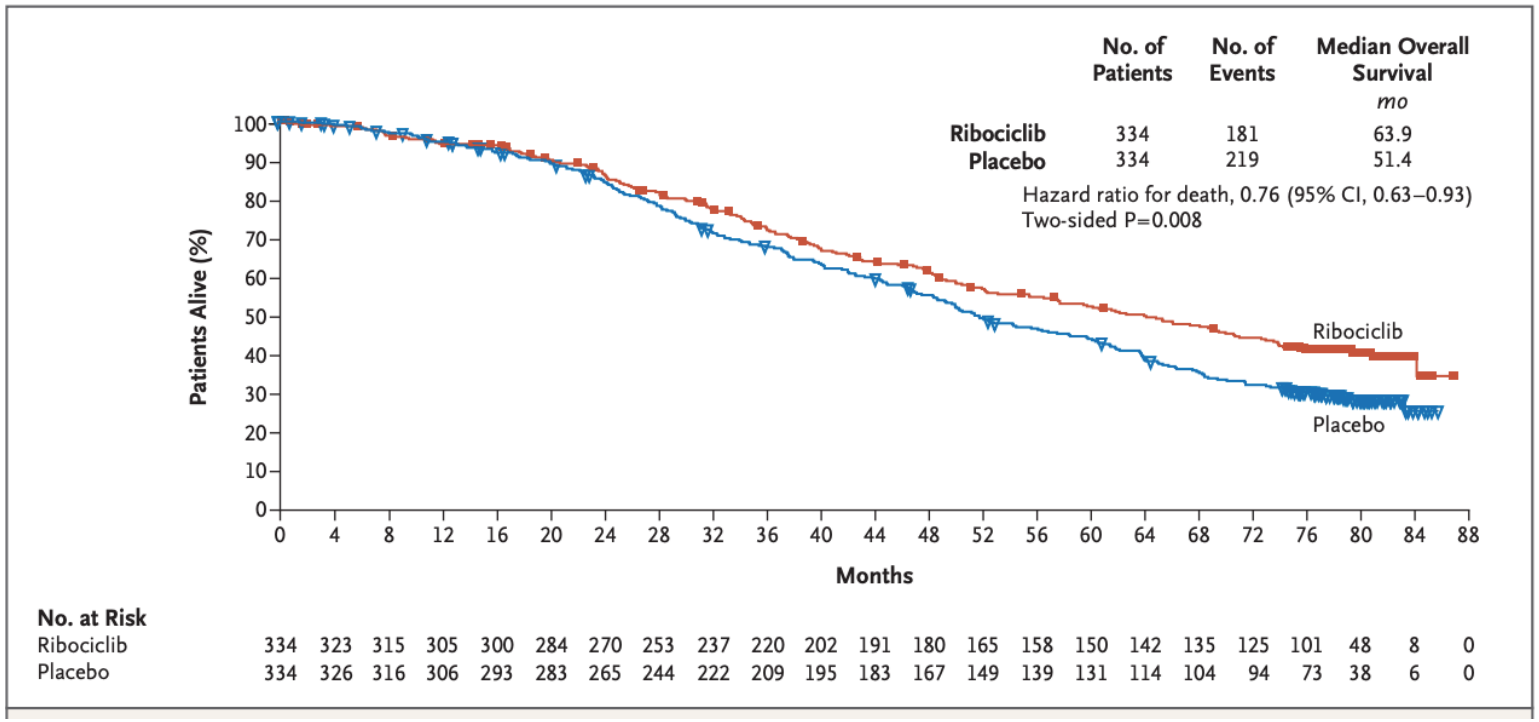
S.-A. Im, Y.-S. Lu, A. Bardia, N. Harbeck, M. Colleoni, F. Franke, L. Chow, J. Sohn, K.-S. Lee, S. Campos-Gomez, R. Villanueva-Vazquez, K.-H. Jung, A. Chakravartty, G. Hughes, I. Gounaris, K. Rodriguez-Lorenc, T. Taran, S. Hurvitz, and D. Tripathy



ORIGINAL ARTICLE

Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer

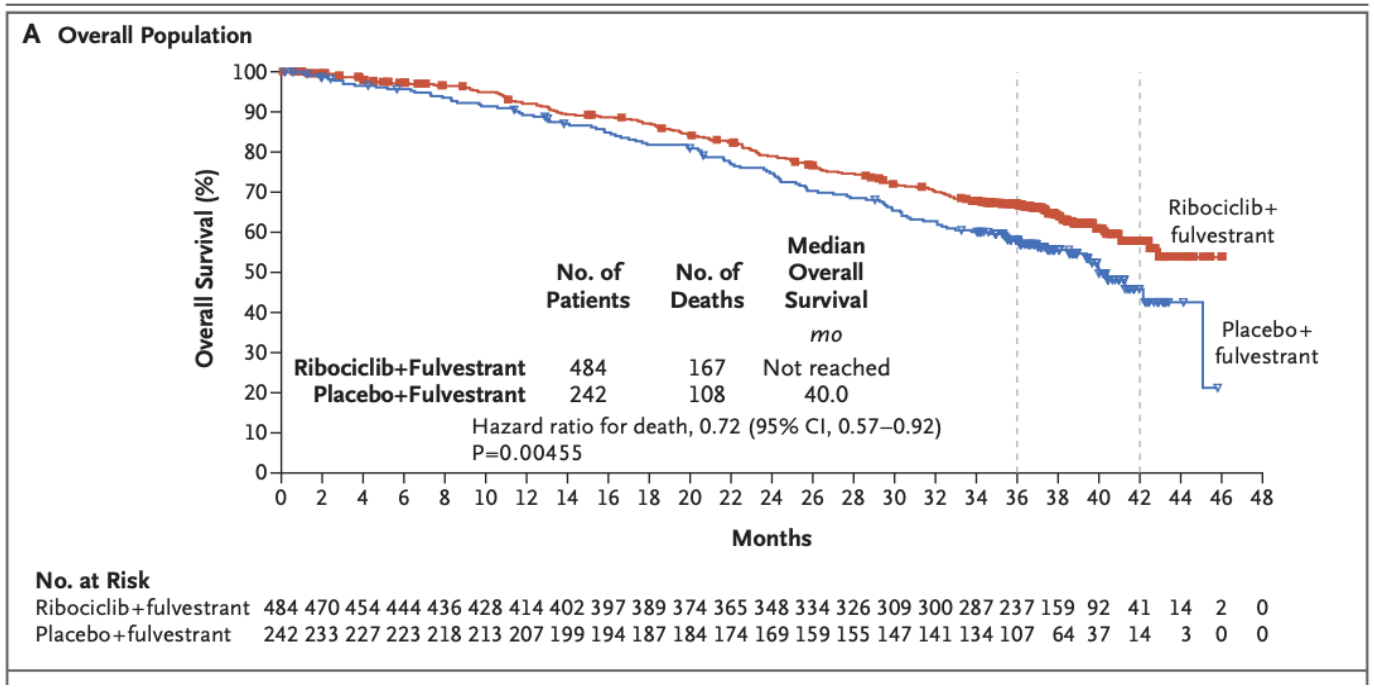
Gabriel N. Hortobagyi, M.D., Salomon M. Stemmer, M.D., Howard A. Burris, M.D., Yoon-Sim Yap, M.D., Gabe S. Sonke, M.D., Ph.D., Lowell Hart, M.D., Mario Campone, M.D., Ph.D., Katarina Petrakova, M.D., Ph.D., Eric P. Winer, M.D., Wolfgang Janni, M.D., Ph.D., Pierfranco Conte, M.D., Ph.D., David A. Cameron, M.D., Fabrice André, M.D., Ph.D., Carlos L. Arteaga, M.D., Juan P. Zarate, M.D., Arunava Chakravartty, Ph.D., Tetiana Taran, M.D., Fabienne Le Gac, Ph.D., Pharm.D., Paolo Serra, M.Sc., and Joyce O'Shaughnessy, M.D.



ORIGINAL ARTICLE

Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer

Dennis J. Slamon, M.D., Ph.D., Patrick Neven, M.D., Ph.D., Stephen Chia, M.D., Peter A. Fasching, M.D., Michelino De Laurentiis, M.D., Ph.D., Seock-Ah Im, M.D., Ph.D., Katarina Petrakova, M.D., Ph.D., Giulia V. Bianchi, M.D., Francisco J. Esteva, M.D., Ph.D., Miguel Martín, M.D., Ph.D., Arnd Nusch, M.D., Gabe S. Sonke, M.D., Ph.D., Luis De la Cruz-Merino, M.D., Ph.D., J. Thaddeus Beck, M.D., Xavier Pivot, M.D., Ph.D., Manu Sondhi, M.D., M.P.H., Yingbo Wang, Ph.D., Arunava Chakravartty, Ph.D., Karen Rodriguez-Lorenc, M.D., Tetiana Taran, M.D., and Guy Jerusalem, M.D., Ph.D.

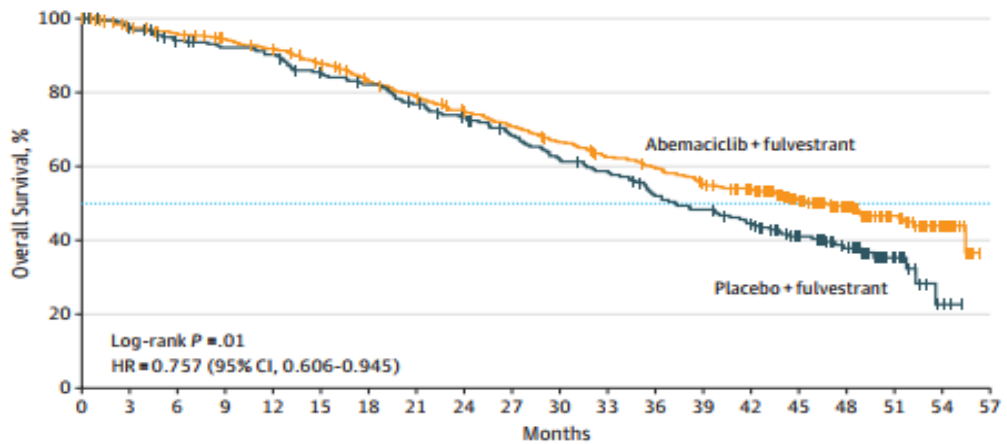


JAMA Oncology | Original Investigation

The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor–Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy—MONARCH 2
A Randomized Clinical Trial

George W. Sledge Jr, MD; Masakazu Toi, MD, PhD; Patrick Neven, MD, PhD; Joohyuk Sohn, MD; Kenichi Inoue, MD, PhD; Xavier Pivot, MD, PhD; Olga Burdaeva, MD; Meena Okera, MD; Norikazu Masuda, MD, PhD; Peter A. Kaufman, MD; Han Koh, MD; Eva-Maria Grischke, MD; PierFranco Conte, MD; Yi Lu, PhD; Susana Barriga, PhD; Karla Hurt, BSN; Martin Frenzel, PhD; Stephen Johnston, MD, PhD; Antonio Llombart-Cussac, MD, PhD

Figure 2. Kaplan-Meier Curve of Overall Survival in the Intent-to-Treat Population



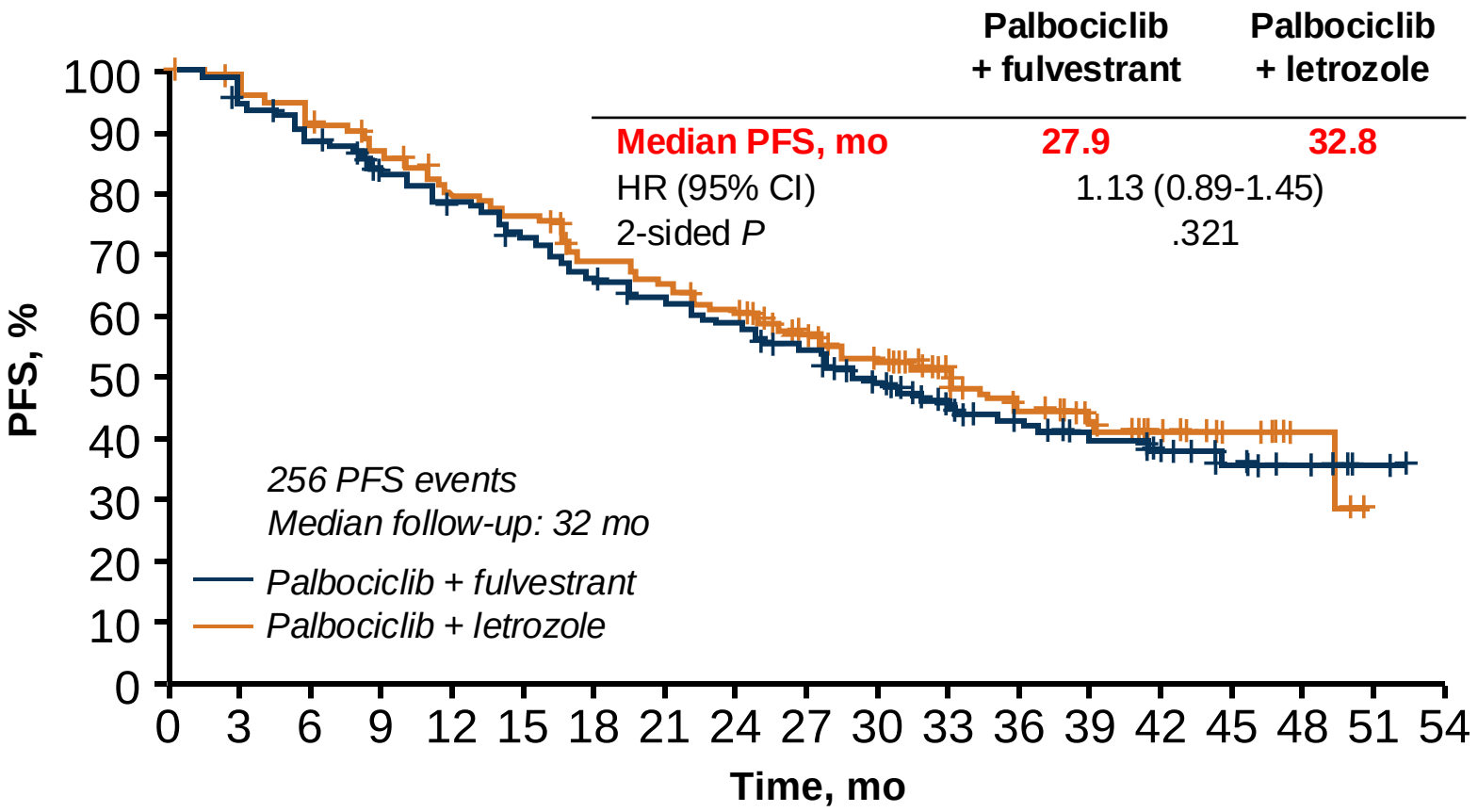
No. at risk

Abemaciclib + fulvestrant	446	422	410	397	384	364	339	321	302	284	265	246	234	214	202	157	101	58	23	0
Placebo + fulvestrant	223	214	201	195	191	178	170	158	148	135	122	115	99	92	82	62	42	15	3	0

The number of events in the abemaciclib plus fulvestrant arm was 211 vs 127 in the placebo plus fulvestrant arm. Median overall survival in the abemaciclib plus fulvestrant arm was 46.7 months vs 37.3 months in the placebo plus fulvestrant arm. HR indicates hazard ratio.

CDKi+Ai versus CDKi+SERD

PARSIFAL: AI or Fulvestrant as Choice of ET in Combination With Palbociclib in First-Line Setting



Outcome, %	Palbociclib + Fulvestrant (n = 243)	Palbociclib + Letrozole (n = 243)
Efficacy		
3-y OS[a]	79.4	77.1
ORR	46.5	50.2
CBR	70.8	69.1
Safety	289	140
Grade 3/4 TRAEs	70.5	70.1
Discontinued due to AEs	5.4	2.1

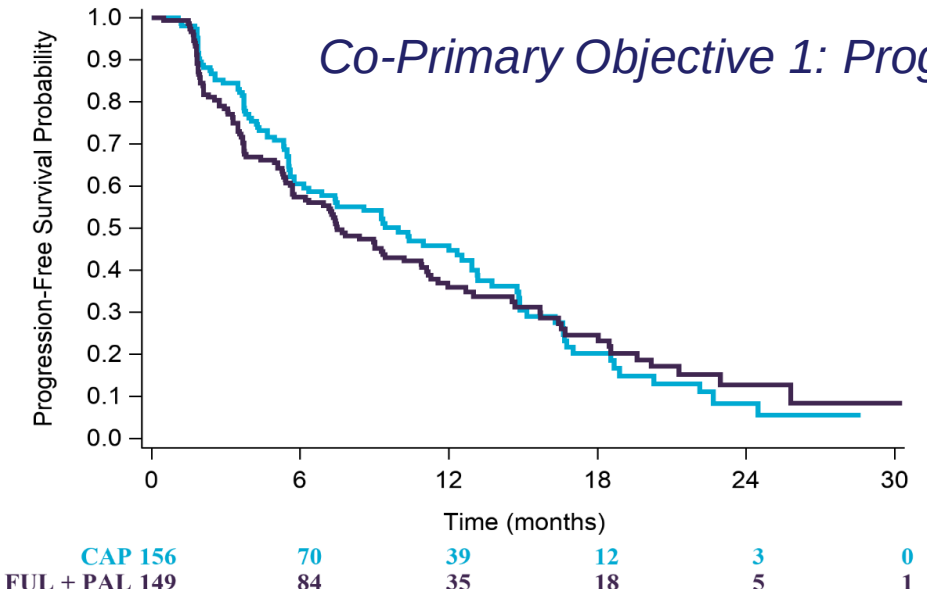
- *Study did not demonstrate either superiority or noninferiority of fulvestrant + palbociclib vs letrozole+ palbociclib (noninferiority margin: HR of 1.21 for PFS)*
  - *No PFS differences in subgroups defined by visceral involvement, de novo vs recurrent metastatic disease*

Llombart-Cussac A et al. JAMA Oncol. 2021;7(12):1791-1799.

CDKi+ET versus Chemotherapy

PEARL study (GEICAM/2013-02): Results

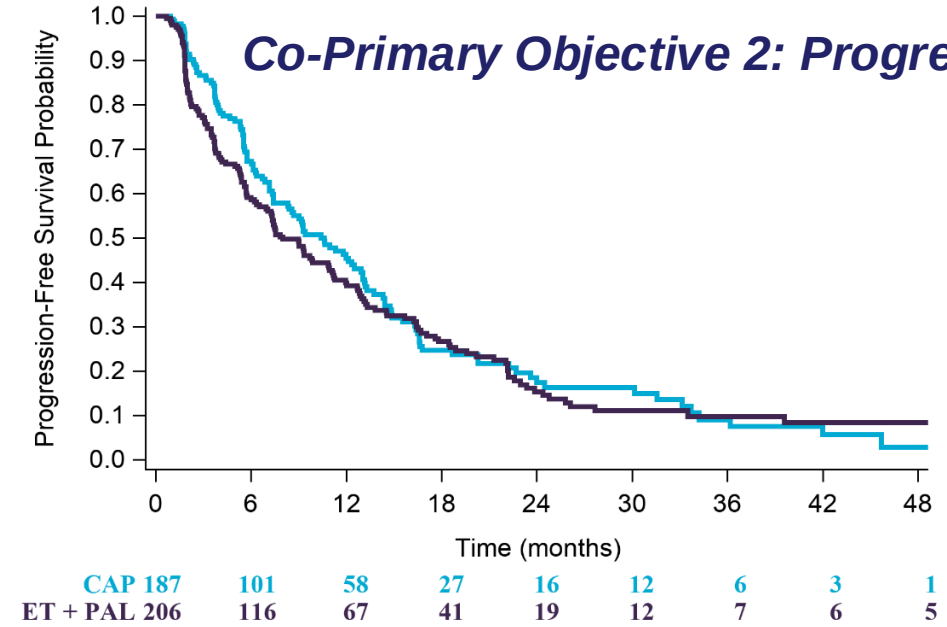
Co-Primary Objective 1: Progression-Free Survival Cohort 2 (N=305)



	FUL + PAL N=149	CAP N=156
Events, n (%)	108 (72.5)	94 (60.3)
Censored, n (%)	41 (27.5)	62 (39.7)
Median PFS, months (95% CI)	7.5 (5.7, 10.9)	10.0 (6.3, 12.9)
Adjusted Hazard Ratio (95% CI)	1.09 (0.83, 1.44)	
Adjusted p-value (Cox)	0.537	

The adjusted hazard ratio was obtained using a stratified Cox proportional hazard model with treatment arm and the stratification factors as covariates

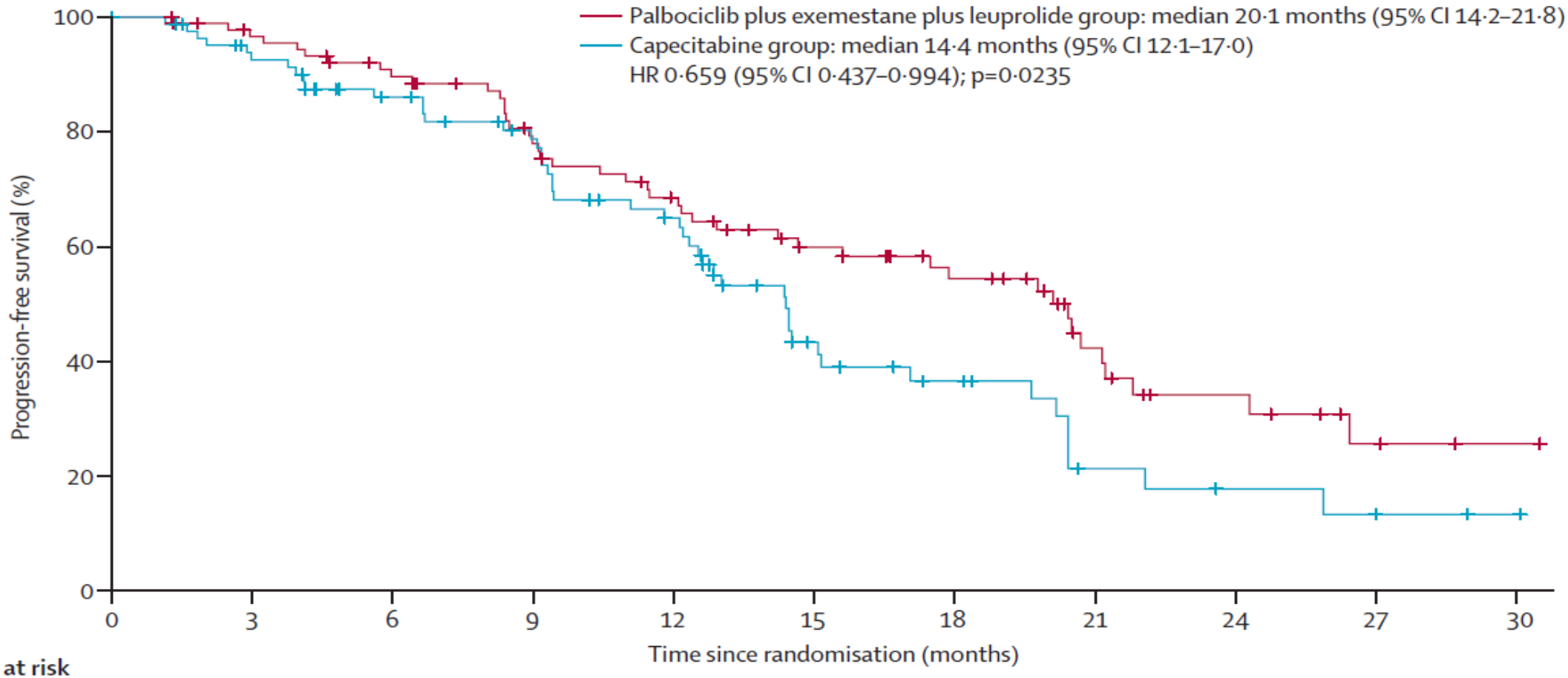
Co-Primary Objective 2: Progression-Free Survival ESR1 Wild type (N=393)



	ET + PAL/ESR1 wt N=206	CAP N=187
Events, n (%)	161 (78.2)	126 (67.4)
Censored, n (%)	45 (21.8)	61 (32.6)
Median PFS, months (95% CI)	8.0 (6.5, 10.9)	10.6 (7.4, 13.0)
Adjusted Hazard Ratio (95% CI)	1.08 (0.85, 1.36)	
Adjusted p-value (Cox)	0.526	

Martin M et al. Ann Oncol. 2021;32(4):488-499.

Young Pearl Study: Palbociclib/Exemestane/Leuprolide vs Capecitabine

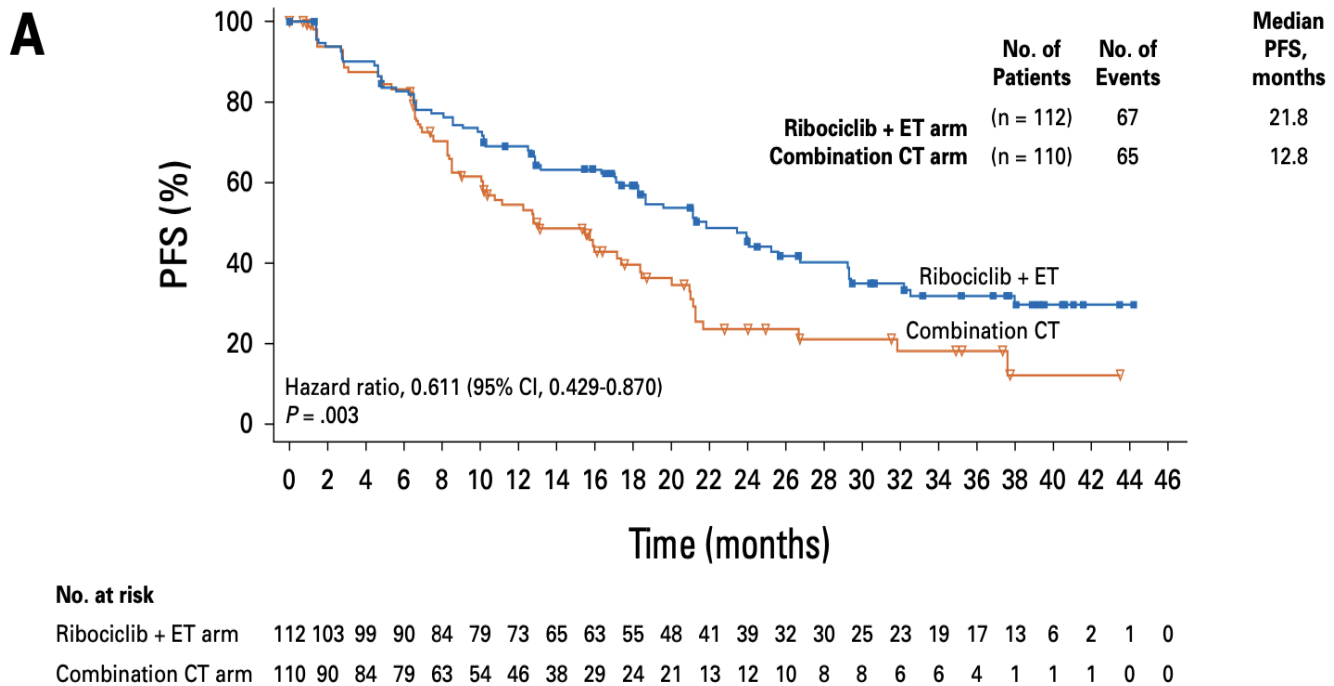


Number at risk (number censored)													
Palbociclib plus exemestane plus leuprolide group	92 (0)	89 (2)	85 (4)	82 (4)	74 (9)	59 (15)	49 (18)	38 (23)	28 (30)	16 (37)	10 (40)	5 (43)	2 (46)
Capecitabine group	83 (3)	81 (4)	73 (7)	65 (11)	61 (14)	52 (18)	40 (21)	20 (29)	14 (32)	6 (35)	4 (36)	2 (37)	1 (38)

Park YH et al. Lancet Oncol. 2019;20(12):1750-1759.

Final Results of RIGHT Choice: Ribociclib Plus Endocrine Therapy Versus Combination Chemotherapy in Premenopausal Women With Clinically Aggressive Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer

Yen-Shen Lu, MD, PhD[1]; Eznal Izwadi Bin Mohd Mahidin, MD[2]; Hamdy Azim, MD[3]; Yesim Eralp, MD[4]; Yoon Sim Yap, MD, PhD[5]; Seock-Ah Im, MD, PhD[6]; Julie Rihani[7]; Erhan Gokmen, MD, PhD[8]; Ahmed El Bastawisy, MD[9]; Nuri Karadurmus, MD[10]; Yueh Ni Lim, MD[11]; Chun Sen Lim, MD[12]; Le Thanh Duc, MD[13]; Wei-Pang Chung, MD[14]; K. Govind Babu, MD[15]; Konstantin Penkov, MD[16]; James Bowles, BMedSci[17]; Teresa Delgar Alfaro, PharmD, MSc[17]; Jiwen Wu, PhD[18]; Melissa Gao, MD, PhD[17]; Khemaies Slimane, MD[17]; and Nagi S. El Saghir, MD[19]



CDKi after CDK4/6i failure

	MAINTAIN	*PACE*	*PALMIRA*	*PostMONARCH*
Phase	*II*	*II*	*II*	*III*
Sample size	*120 (1:1)*	*220 (1:1:1)*	*198 (2:1)*	*350*
Design	*Fulvestrant or exemestane +/- ribociclib*	*Arm A: Fulvestrant* *Arm B: Fulvestrant + Palbociclib* *Arm C: Fulvestrant + Palbociclib + Avelumab*	*Fulvestrant or letrozole +/- palbociclib*	*Fulvestrant +/- abemaciclib*
HR+ MBC progression on iCDK 4/6+ET				
Initial CDK 4/6 inhibitor	*Palbociclib (84%)* *Ribociclib (11%)*	*Palbociclib (90%)*	*Palbociclib (100%)*	
Continuation iCDK 4/6	*Ribociclib*	*Palbociclib*	*Palbociclib*	*Abemaciclib*
% iCDK > 12mo	*67%*	*75%*	*86%*	
Continuation ET	*Fulvestrant (83%), exemestane (17%)*	*Fulvestrant (100%)*	*Fulvestrant (90%), letrozole (10%)*	
PFS ET+CDK4/6 inhibitor vs. ET	*5.3 vs. 2.8 months (HR 0.56)*	*4.6 vs. 4.8 months (HR 1.11)*	*4.9 vs. 3.6 months (HR 0.84)*	

AI: aromatase inhibitor; CDK: cyclin dependent kinase; ER: endocrine therapy; HER2: human epidermal growth factor receptor 2; HR: hazard ratio; HR+ hormone receptor positive; PFS: progression free survival

Kalinsky K et al. JCO 2023.
Mayer E et al. SABCS 2022.
Llombart-Cussac A et al. ASCO 2023.

2024 ASCO ANNUAL MEETING

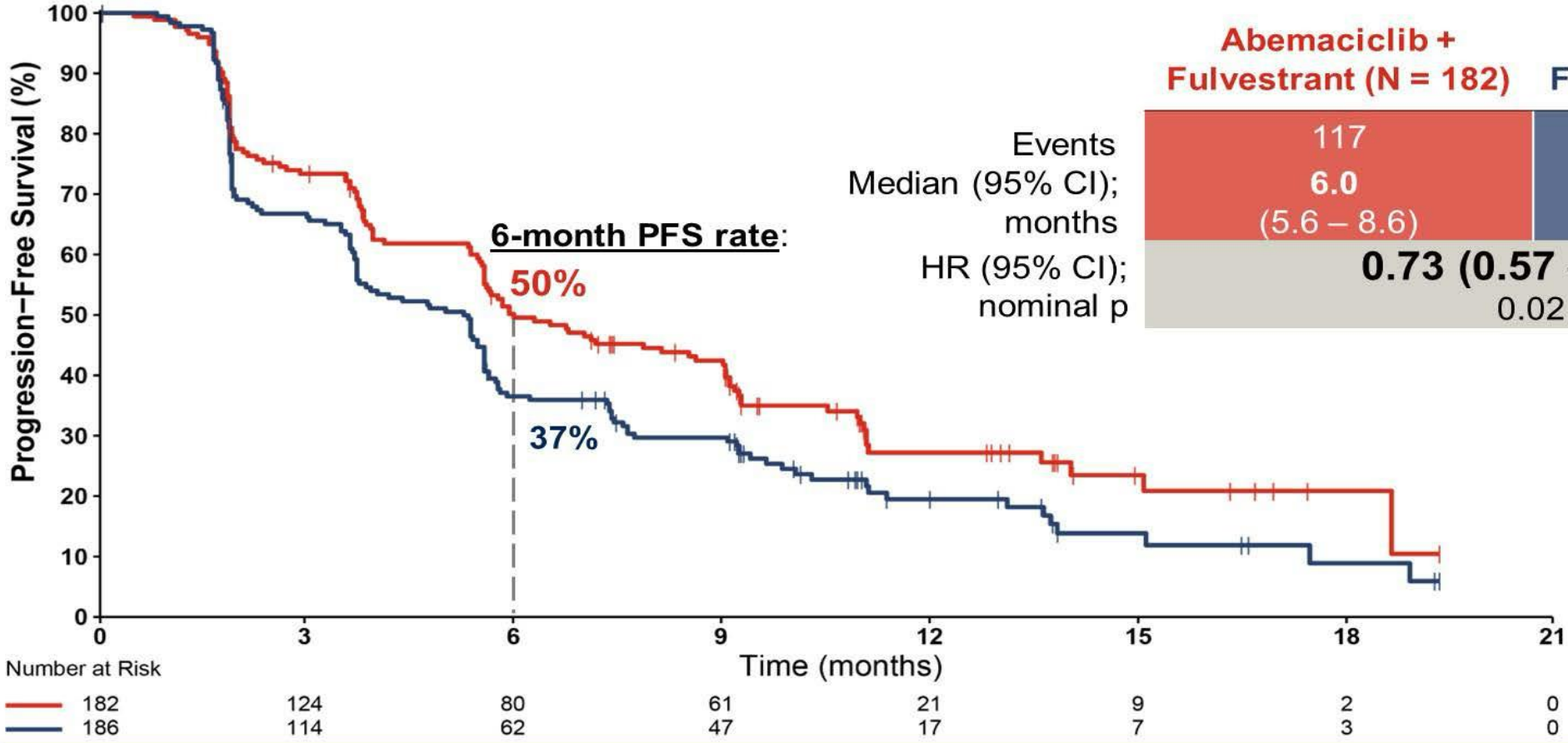
Abemaciclib plus fulvestrant vs fulvestrant alone for HR+, HER2- advanced breast cancer following progression on prior CDK4/6 inhibitor plus endocrine therapy: Primary outcome of the Phase 3 postMONARCH trial

Kevin Kalinsky[1], Giampaolo Bianchini[2], Erika P. Hamilton[3], Stephanie L. Graff[4], Kyong Hwa Park[5], Rinath Jeselsohn[6], Umut Demirci[7], Miguel Martin[8], Rachel M. Layman[9], Sara Hurvitz[10], Sarah Sammons[11], Peter A. Kaufman[12], Montserrat Munoz[13], Ling-Ming Tseng[14], Holly Knoderer[15], Bastien Nguyen[15], Yanhong Zhou[15], Elizabeth Ravenberg[15], Lacey M. Litchfield[15], Seth A. Wander[16]

[1]Winship Cancer Institute at Emory University, Atlanta, GA, USA, [2]IRCCS Ospedale, San Raffaele, Milan, Italy, [3]Sarah Cannon Research Institute, Nashville, TN, USA, [4]Lifespan Cancer Institute, Warren Albert School of Medicine, Brown University, Providence, RI, USA , [5]Korea University Anam Hospital, Korea University, Seoul, South Korea, [6]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA, [7]Memorial Ankara Hospital, Ankara, Turkey, [8]Hospital General Universitario Gregorio Maranon, Universidad Complutense, Madrid, Spain, [9]MD Anderson Cancer Center, University of Texas, Houston, TX, USA, [10]Fred Hutchinson Cancer Center, University of Washington School of Medicine, Seattle, WA, USA, [11]Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA, [12]University of Vermont Medical Center, Burlington, VT, USA, [13]Hospital Clinic i Provincial, Barcelona, Spain,[14]Taipei Veterans General Hospital, Taipei, Taiwan,[15]Eli Lilly and Company, Indianapolis, IN, USA, [16]Massachusetts General Hospital, Harvard University, Boston, MA, USA

PRESENTED BY: Kevin Kalinsky, MD, MS

Primary Analysis: Abemaciclib Improved Investigator-Assessed PFS

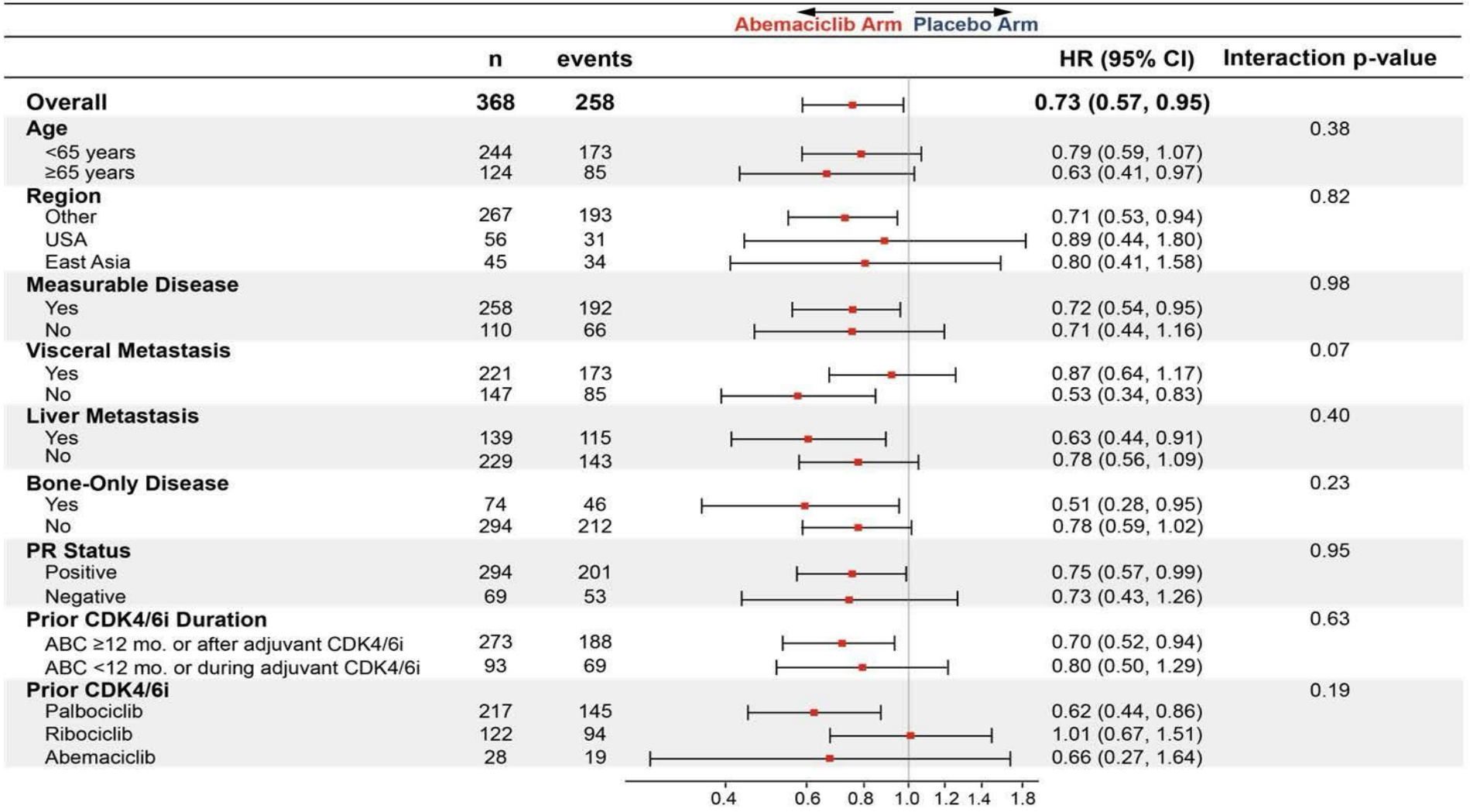


	Abemaciclib + Fulvestrant (N = 182)	Placebo + Fulvestrant (N = 186)
Events	117	141
Median (95% CI); months	**6.0** (5.6 – 8.6)	**5.3** (3.7 – 5.6)
HR (95% CI); nominal p	**0.73 (0.57 – 0.95)** 0.02	

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

PRESENTED BY: Kevin Kalinsky, MD, MS

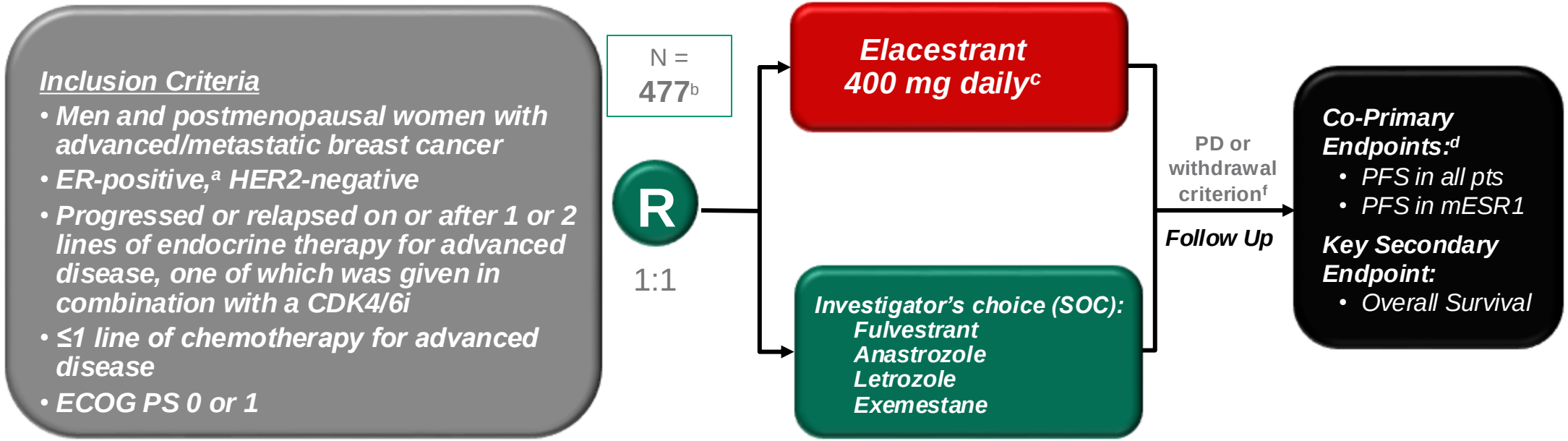
Investigator-Assessed PFS by Subgroup: Consistent Abemaciclib Effect Across Subgroups



Targeted Therapy in Metastatic Breast Cancer

ESR-1+

EMERALD Phase 3 Study Design



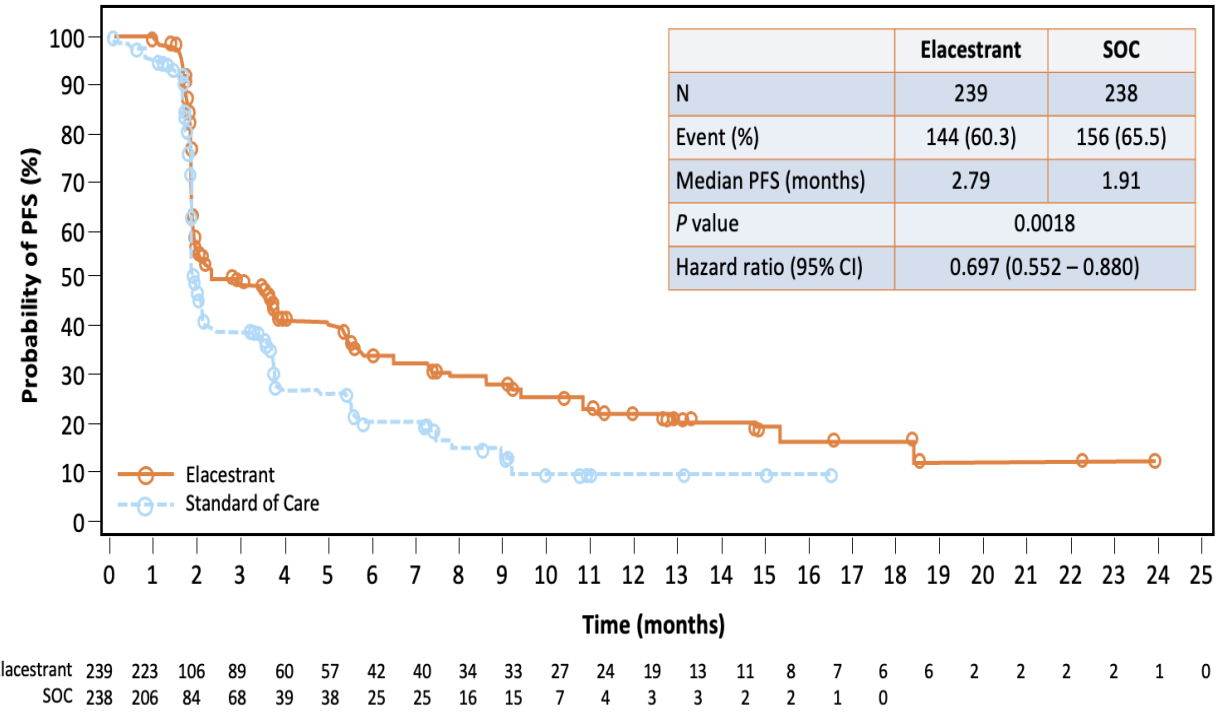
[a]*Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry;* [b]*Recruitment from February 2019 to October 2020;* [c]*Protocol-defined dose reductions permitted;* [d]*Blinded Independent Central Review.* [e]*ESR1-mutation status was determined by ctDNA analysis using the Guardant360 assay (* *´Restaging CT scans every 8 weeks.*

CBR, clinical benefit rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival, PD, progressive disease; PFS: progression-free survival; Pts, patients; R, randomized. SOC, standard of care.

Bidard FC. J Clin Oncol. 2022;40(28):3246-3256.

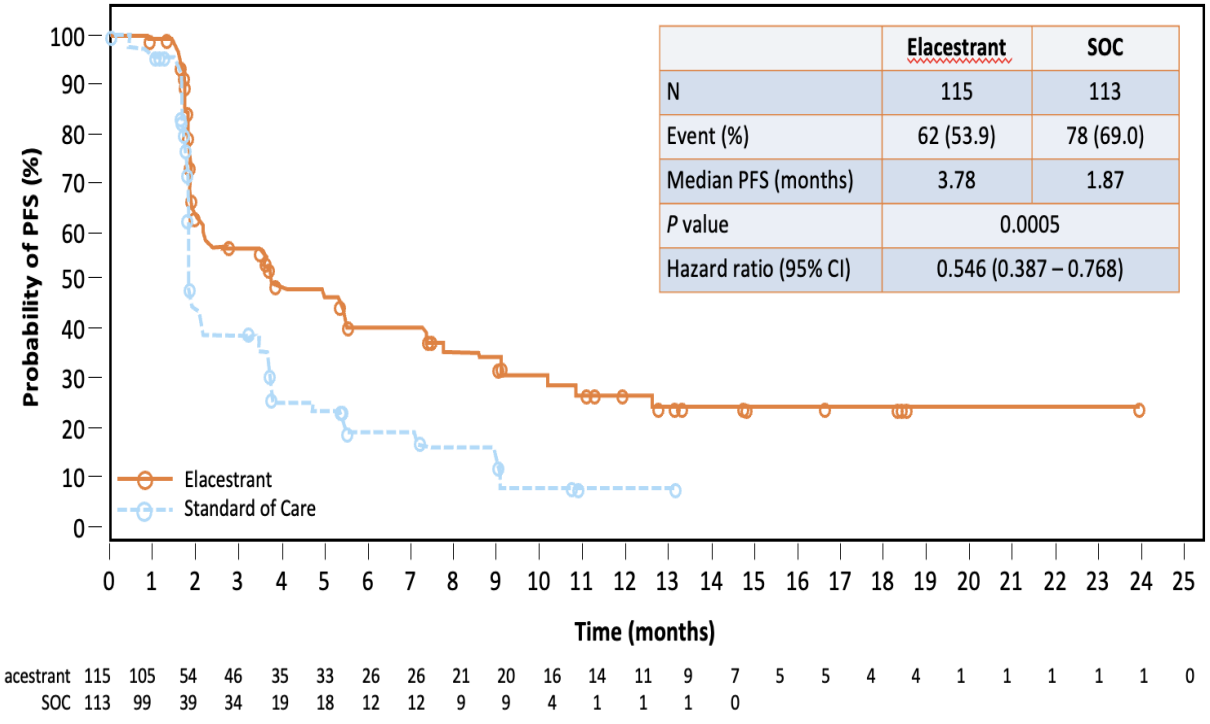
Primary Endpoint: PFS by IRC

All Patients (ITT)



	Elacestrant	SOC
N	239	238
Event (%)	144 (60.3)	156 (65.5)
Median PFS (months)	2.79	1.91
P value	0.0018	
Hazard ratio (95% CI)	0.697 (0.552 – 0.880)	

Patients With Tumors Harboring mESR1



	Elacestrant	SOC
N	115	113
Event (%)	62 (53.9)	78 (69.0)
Median PFS (months)	3.78	1.87
P value	0.0005	
Hazard ratio (95% CI)	0.546 (0.387 – 0.768)	

Bidard FC. J Clin Oncol. 2022;40(28):3246-3256.

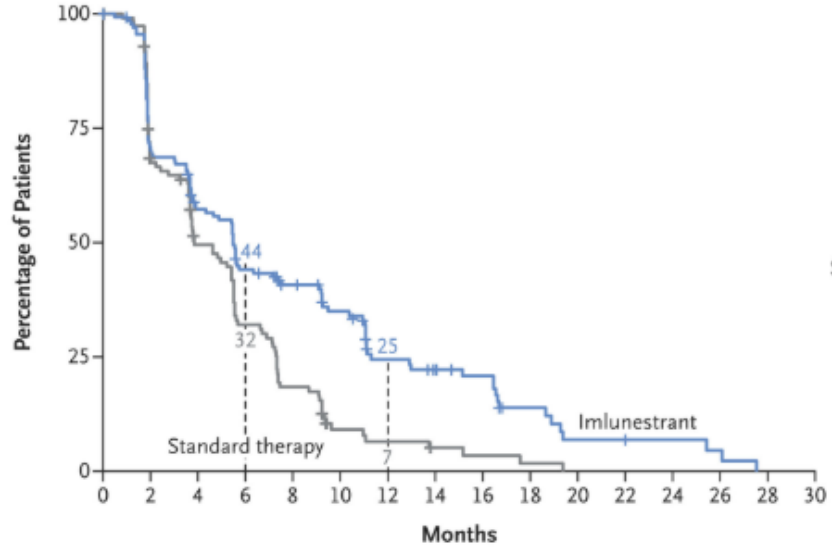
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Imlunestrant with or without Abemaciclib in Advanced Breast Cancer

K.L. Jhaveri, P. Neven, M.L. Casalnuovo, S.-B. Kim, E. Tokunaga, P. Aftimos, C. Saura, J. O'Shaughnessy, N. Harbeck, L.A. Carey, G. Curigliano, A. Llombart-Cussac, E. Lim, M...L. García Tinoco, J. Sohn, A. Mattar, Q. Zhang, C.-S. Huang, C.-C. Hung, J.L. Martinez Rodriguez, M. Ruíz Borrego, R. Nakamura, K.R. Pradhan, C. Cramer von Laue, E. Barrett, S. Cao, X.A. Wang, L.M. Smyth, and F.-C. Bidard, for the EMBER-3 Study Group*

A Progression-free Survival among Patients with *ESR1* Mutations, Imlunestrant vs. Standard Therapy

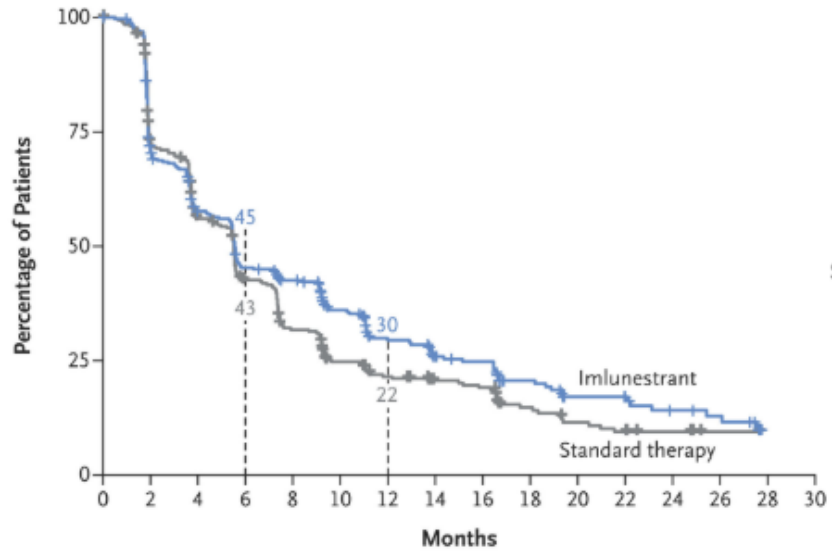


No. at Risk																
Imlunestrant	138	95	74	56	45	35	22	18	15	8	4	4	3	2	0	0
Standard therapy	118	74	51	33	19	7	5	3	2	1	0	0	0	0	0	0

	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Imlunestrant	138	109	5.5 (3.9–7.4)
Standard Therapy	118	102	3.8 (3.7–5.5)

Difference in restricted mean survival time, 2.6 mo (95% CI, 1.2–3.9)
P<0.001

B Progression-free Survival among All Patients, Imlunestrant vs. Standard Therapy

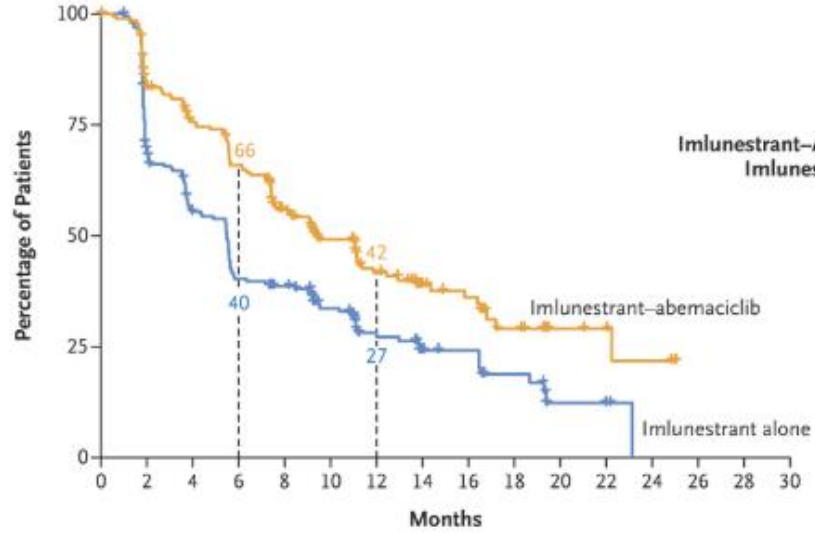


No. at Risk																
Imlunestrant	331	225	173	135	118	89	62	47	43	30	20	19	13	10	0	0
Standard therapy	330	221	165	122	89	63	51	41	38	23	17	14	10	2	0	0

	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Imlunestrant	331	237	5.6 (5.3–7.3)
Standard Therapy	330	253	5.5 (4.6–5.6)

Hazard ratio for disease progression or death, 0.87 (95% CI, 0.72–1.04)
P=0.12

A Progression-free Survival among All Patients, Imlunestrant–Abemaciclib vs. Imlunestrant Alone

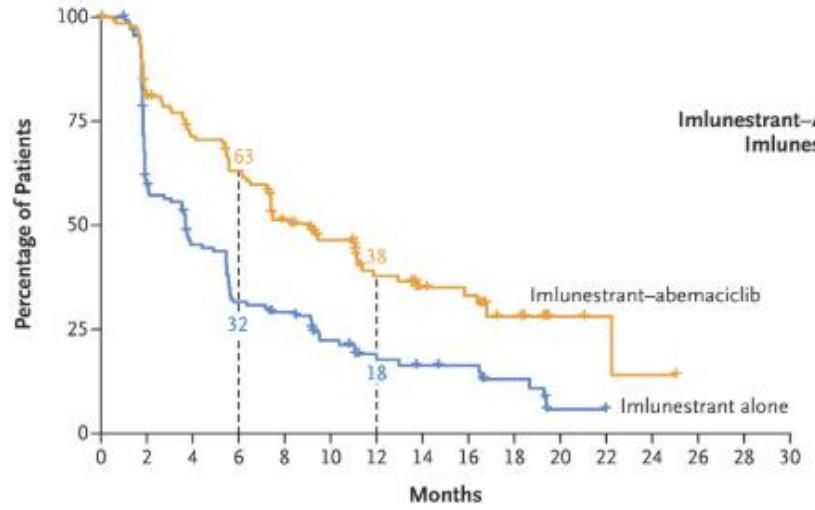


	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Imlunestrant–Abemaciclib	213	114	9.4 (7.5–11.9)
Imlunestrant Alone	213	149	5.5 (3.8–5.6)

Hazard ratio for disease progression or death, 0.57 (95% CI, 0.44–0.73)
P<0.001

No. at Risk																
Imlunestrant–abemaciclib	213	165	141	122	96	72	48	29	25	13	6	5	3	0	0	0
Imlunestrant alone	213	140	106	77	67	48	29	20	18	10	3	2	0	0	0	0

B Progression-free Survival among Patients with Previous CDK4/6 Inhibitor Treatment, Imlunestrant–Abemaciclib vs. Imlunestrant Alone



	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Imlunestrant–Abemaciclib	139	79	9.1 (7.2–11.2)
Imlunestrant Alone	140	109	3.7 (2.1–5.5)

Hazard ratio for disease progression or death, 0.51 (95% CI, 0.38–0.68)

No. at Risk																
Imlunestrant–abemaciclib	139	105	87	76	58	43	29	19	17	8	3	2	1	0	0	0
Imlunestrant alone	140	79	56	39	32	21	13	11	10	6	1	0	0	0	0	0

Targeted Therapy in Metastatic Breast Cancer

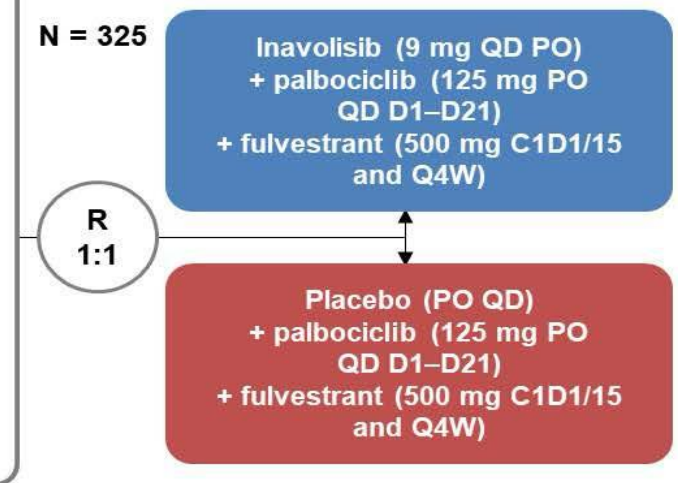
CDKi+ET+ PIK3CAi, versus CDKi+ET
First-line and Second/Third-line

INAVO120 study design[1]

Key eligibility criteria

Enrichment of patients with poor prognosis:

- ***PIK3CA*-mutated, HR+, HER2– LA/mBC** by central ctDNA or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**
- **Fasting glucose <126 mg/dL (<7.0 mmol/L) and HbA1c <6.0% (< 42 mmol/mol)**



Statistical methods

- For efficacy endpoints and TTCD, hazard ratios were estimated using a Cox proportional hazard model with 95% CI and Kaplan–Meier methodology was used to estimate the medians with the Brookmeyer–Crowley method used for the 95% CI

Efficacy endpoints

- PFS by investigator
- OS
- ORR, BOR, CBR, DOR
- **Time from randomization to end or discontinuation of next-line treatment, or death from any cause (proxy for PFS2)**
- **Time from randomization to first subsequent chemotherapy after treatment discontinuation**

Safety endpoints

Key selected AEs (hyperglycemia, diarrhea, rash, and stomatitis/mucosal inflammation)*

Patient-reported outcomes endpoints†

- **BPI-SF: TTCD in worse pain‡§**
- **EORTC QLQ-C30: mean change from baseline in HRQoL, physical functioning, and role functioning‖**
- **PRO-CTCAE: presence, frequency of occurrence, severity, and/or degree of interference with daily function of selected symptomatic treatment toxicities**
- **An overall bother item: overall bother experienced due to side effects of treatment**

* Assessed using grouped terms; severity reported per National Cancer Institute CTCAE version 5.0. † Assessed at D1 of C1–3 then D1 of every other C thereafter (5, 7, 9, etc.), at treatment discontinuation, and every 3 months during survival follow-up; baseline completion rates in both arms were >90% for all assessments; post-baseline rates in both arms remain >80% through C15; <50% intent-to-treat sample remaining at C9 in the inavolisib arm versus C5 in the placebo arm. ‡ Type I error-controlled; hierarchically tested according to a prespecified fixed order of endpoints. § Defined as the time from randomization to the first documentation of a ≥2-point increase from baseline on the "worst pain" item held for at least two consecutive Cs, or an initial increase followed by death or treatment discontinuation within 3 weeks from the last assessment. ‖ A ≥10-point change was defined as a clinically meaningful difference.

AE, adverse event; (LA/m)BC, (locally advanced/metastatic) breast cancer; BOR, best overall response; BPI-SF, brief pain inventory-short form; C, Cycle; CBR, clinical benefit rate; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; ctDNA, circulating tumor DNA; D, Day; DOR, duration of response; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; ET, endocrine therapy; HER2–, HER2-negative; HR+, hormone receptor-positive; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, time from randomization to next progression after discontinuing study treatment for PD, or death from any cause; PO, orally; PRO, patient-reported outcomes; Q4W, every 4 weeks; QD, once daily; R, randomized; TTCD, time to confirmed clinical meaningful deterioration.

1. Jhaveri KL, *et al.* SABCS 2023 (Abstract GS03-13).

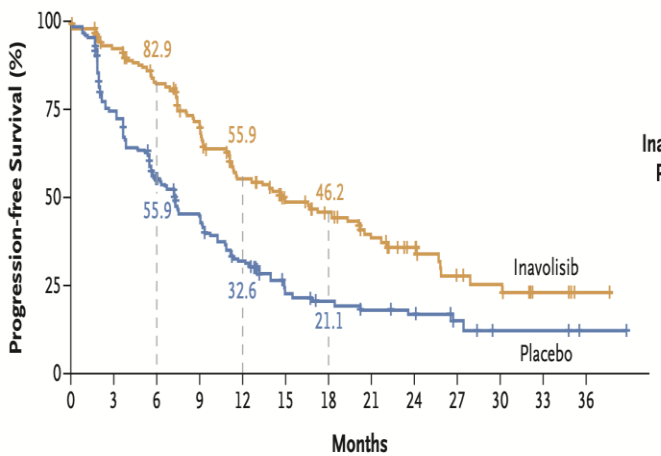
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inavolisib-Based Therapy in *PIK3CA*-Mutated Advanced Breast Cancer

N.C. Turner, S.-A. Im, C. Saura, D. Juric, S. Loibl, K. Kalinsky, P. Schmid, S. Loi, P. Sunpaweravong, A. Musolino, H. Li, Q. Zhang, Z. Nowecki, R. Leung, E. Thanopoulou, N. Shankar, G. Lei, T.J. Stout, K.E. Hutchinson, J.L. Schutzman, C. Song, and K.L. Jhaveri

A Progression-free Survival in the Full Analysis Population

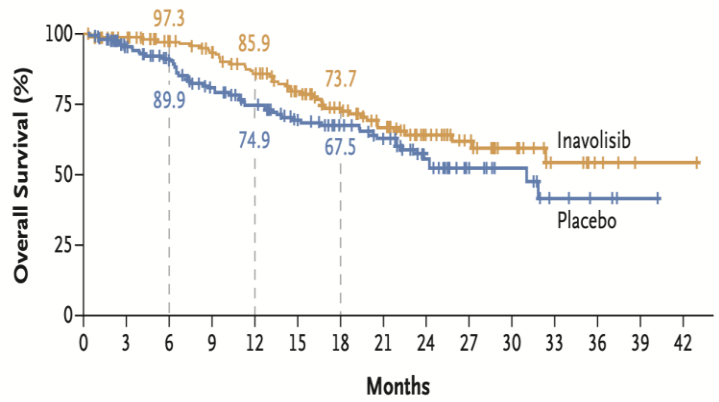


	No. of Events (%)	Median Progression-free Survival (95% CI)
		mo
Inavolisib (N=161)	82 (50.9)	15.0 (11.3–20.5)
Placebo (N=164)	113 (68.9)	7.3 (5.6–9.3)

Stratified hazard ratio for disease progression or death, 0.43 (95% CI, 0.32–0.59)
P<0.001

No. at Risk

Inavolisib	161	134	111	92	66	48	41	31	22	13	11	5	1
Placebo	164	113	77	59	40	23	19	16	12	6	3	3	1



	No. of Deaths (%)	Median Overall Survival (95% CI)
		mo
Inavolisib (N=161)	42 (26.1)	NR (27.3–NR)
Placebo (N=164)	55 (33.5)	31.1 (22.3–NR)

Stratified hazard ratio for death, 0.64 (95% CI, 0.43–0.97)
P=0.03

No. at Risk

Inavolisib	161	143	127	114	101	85	69	56	38	26	17	8	4	1	1
Placebo	164	139	120	98	87	72	61	52	33	19	11	5	3	1	0

Adverse Event	Inavolisib (N=162)		Placebo (N=162)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Neutropenia	144 (88.9)	130 (80.2)	147 (90.7)	127 (78.4)
Thrombocytopenia	78 (48.1)	23 (14.2)	73 (45.1)	7 (4.3)
Stomatitis and mucosal inflammation	83 (51.2)	9 (5.6)	43 (26.5)	0
Anemia	60 (37.0)	10 (6.2)	59 (36.4)	3 (1.9)
Hyperglycemia	95 (58.6)	9 (5.6)	14 (8.6)	0
Diarrhea	78 (48.1)	6 (3.7)	26 (16.0)	0
Nausea	45 (27.8)	1 (0.6)	27 (16.7)	0
Rash	41 (25.3)	0	28 (17.3)	0
Decreased appetite	38 (23.5)	0	14 (8.6)	0
Fatigue	38 (23.5)	0	21 (13.0)	2 (1.2)
Covid-19	37 (22.8)	3 (1.9)	17 (10.5)	1 (0.6)
Headache	34 (21.0)	0	22 (13.6)	0
Leukopenia	28 (17.3)	11 (6.8)	40 (24.7)	17 (10.5)
Ocular toxic effects	36 (22.2)	0	21 (13.0)	0

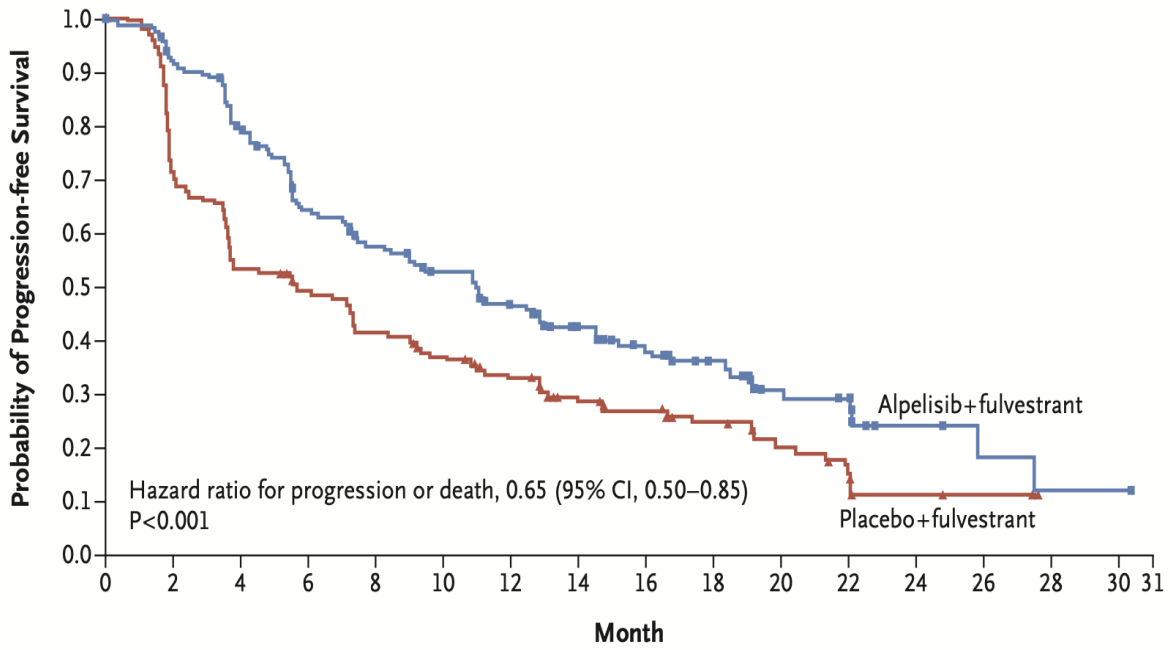
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Alpelisib for *PIK3CA*-Mutated, Hormone Receptor–Positive Advanced Breast Cancer

F. André, E. Ciruelos, G. Rubovszky, M. Campone, S. Loibl, H.S. Rugo, H. Iwata, P. Conte, I.A. Mayer, B. Kaufman, T. Yamashita, Y.-S. Lu, K. Inoue, M. Takahashi, Z. Pápai, A.-S. Longin, D. Mills, C. Wilke, S. Hirawat, and D. Juric, for the SOLAR-1 Study Group*

A Cohort with *PIK3CA*-Mutated Cancer



No. at Risk

Alpelisib+fulvestrant	169	145	123	97	85	75	62	50	39	30	17	14	5	3	1	1	0
Placebo+fulvestrant	172	120	89	80	67	58	48	37	29	20	14	9	3	2	0	0	0

CAPItello-291: Study Design

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

Patients with HR+/HER2– ABC

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

R1:1 (N=708)

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

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

Dual primary endpoints

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

Key secondary endpoints

Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

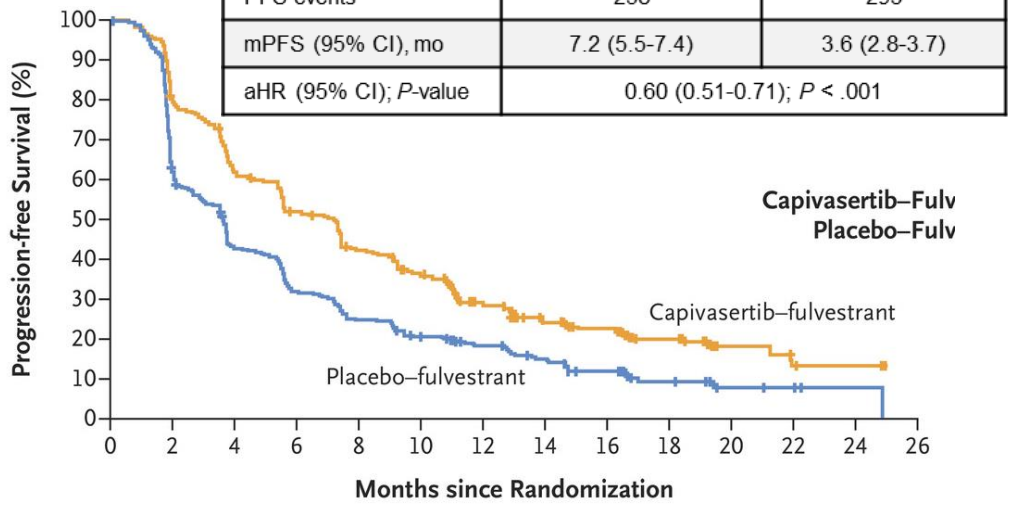
HER2– was defined as IHC 0 or 1+, or IHC 2+/ISH–. *Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia.
ABC, advanced (locally advanced [inoperable] or metastatic) breast cancer.
Pre- or peri-menopausal women also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

Turner NC et al. *N Engl J Med*. 2023;388(22):2058-2070.

CAPItello-291: Dual Primary Endpoint

PFS in overall population

	Capivasertib + fulvestrant (n=355)	Placebo + fulvestrant (n=353)
PFS events	258	293
mPFS (95% CI), mo	7.2 (5.5-7.4)	3.6 (2.8-3.7)
aHR (95% CI); *P*-value	0.60 (0.51-0.71); *P* < .001	

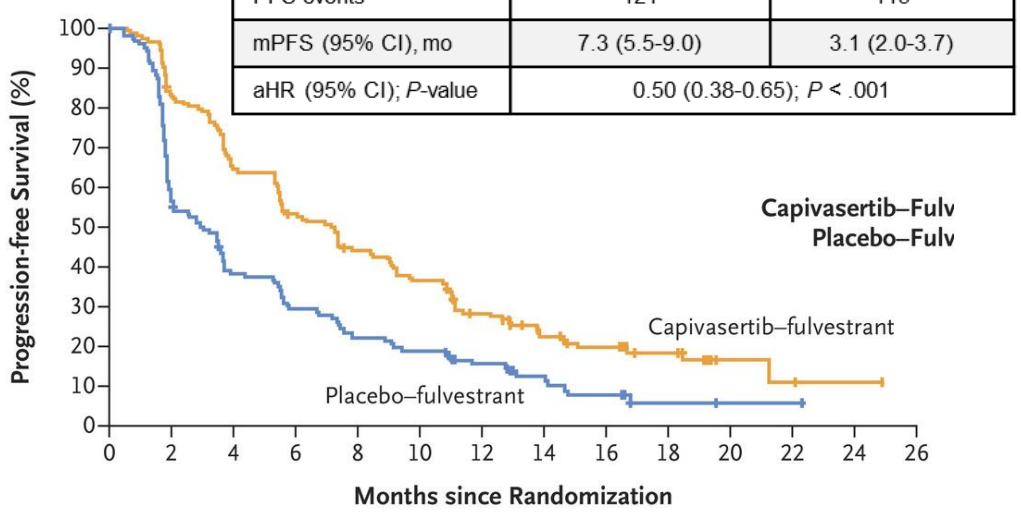


No. at Risk

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

PFS in altered population

	Capivasertib + fulvestrant (n=155)	Placebo + fulvestrant (n=134)
PFS events	121	115
mPFS (95% CI), mo	7.3 (5.5-9.0)	3.1 (2.0-3.7)
aHR (95% CI); *P*-value	0.50 (0.38-0.65); *P* < .001	



No. at Risk

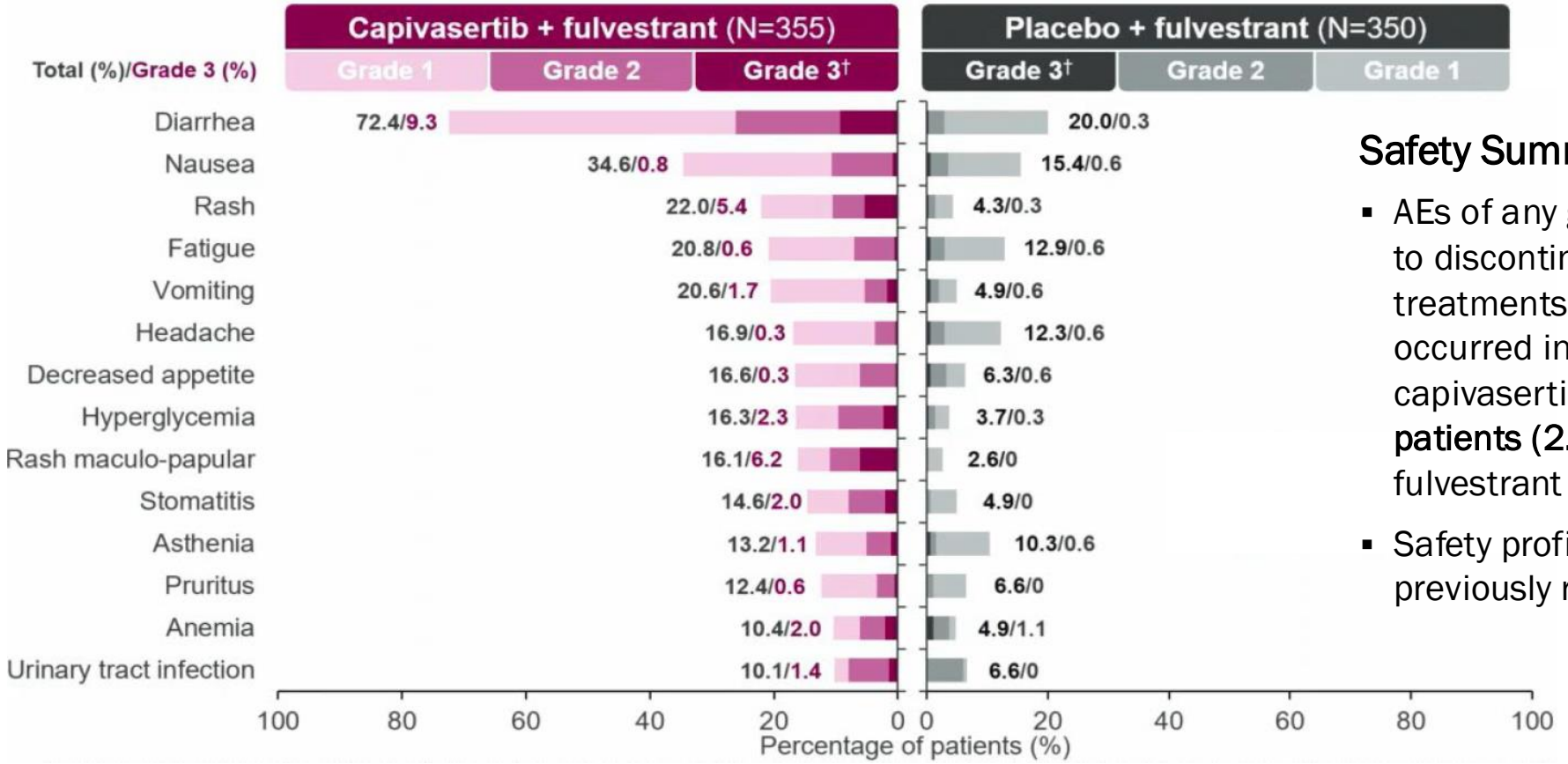
Capivasertib–fulvestrant	155	127	99	80	65	54	38	26	21	12	3	2	1	0
Placebo–fulvestrant	134	77	48	37	28	24	17	11	6	2	1	1	0	0

- PFS benefit was observed in all key subgroups, including regardless of prior use of CDK4/6i and liver metastases

Turner NC et al. *N Engl J Med*. 2023;388(22):2058-2070.

CAPItello-291 Phase 3 Trial of Capivasertib + Fulvestrant in AI-Resistant HR+/HER2– MBC: Safety

AEs (>10% of Patients) in Overall Population



Safety Summary

- AEs of any grade leading to discontinuation of 1 or both treatments in the safety population occurred in **46 patients (13.0%)** in the capivasertib + fulvestrant arm and **8 patients (2.3%)** in the placebo + fulvestrant arm
- Safety profile was consistent with that previously reported

Turner NC, et al. SABCS 2022. Abstract GS3-04.

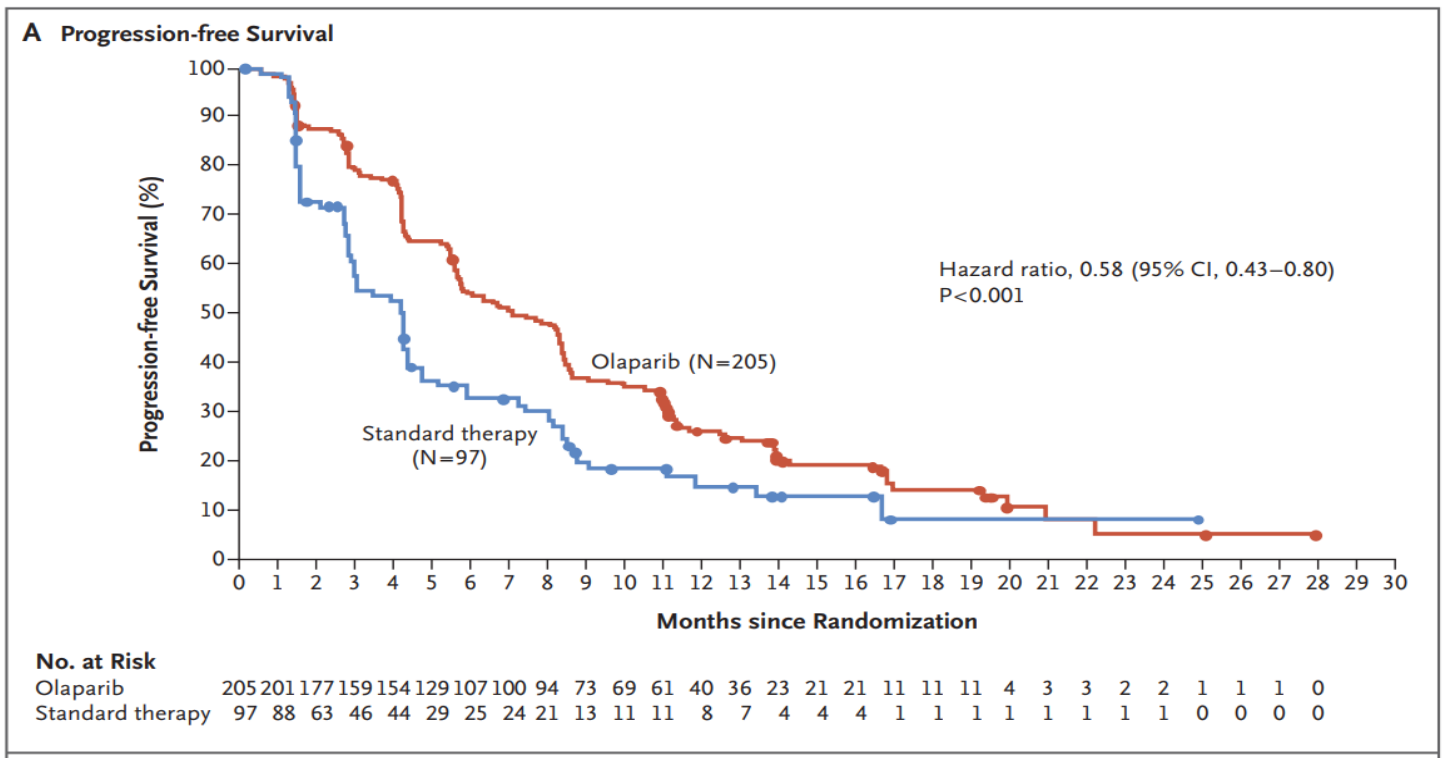
PARP Inhibitors in ER+ Metastatic Breast Cancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Olaparib for Metastatic Breast Cancer in Patients with a Germline *BRCA* Mutation

Mark Robson, M.D., Seock-Ah Im, M.D., Ph.D., Elżbieta Senkus, M.D., Ph.D., Binghe Xu, M.D., Ph.D., Susan M. Domchek, M.D., Norikazu Masuda, M.D., Ph.D., Suzette Delaloge, M.D., Wei Li, M.D., Nadine Tung, M.D., Anne Armstrong, M.D., Ph.D., Wenting Wu, Ph.D., Carsten Goessl, M.D., Sarah Runswick, Ph.D., and Pierfranco Conte, M.D.

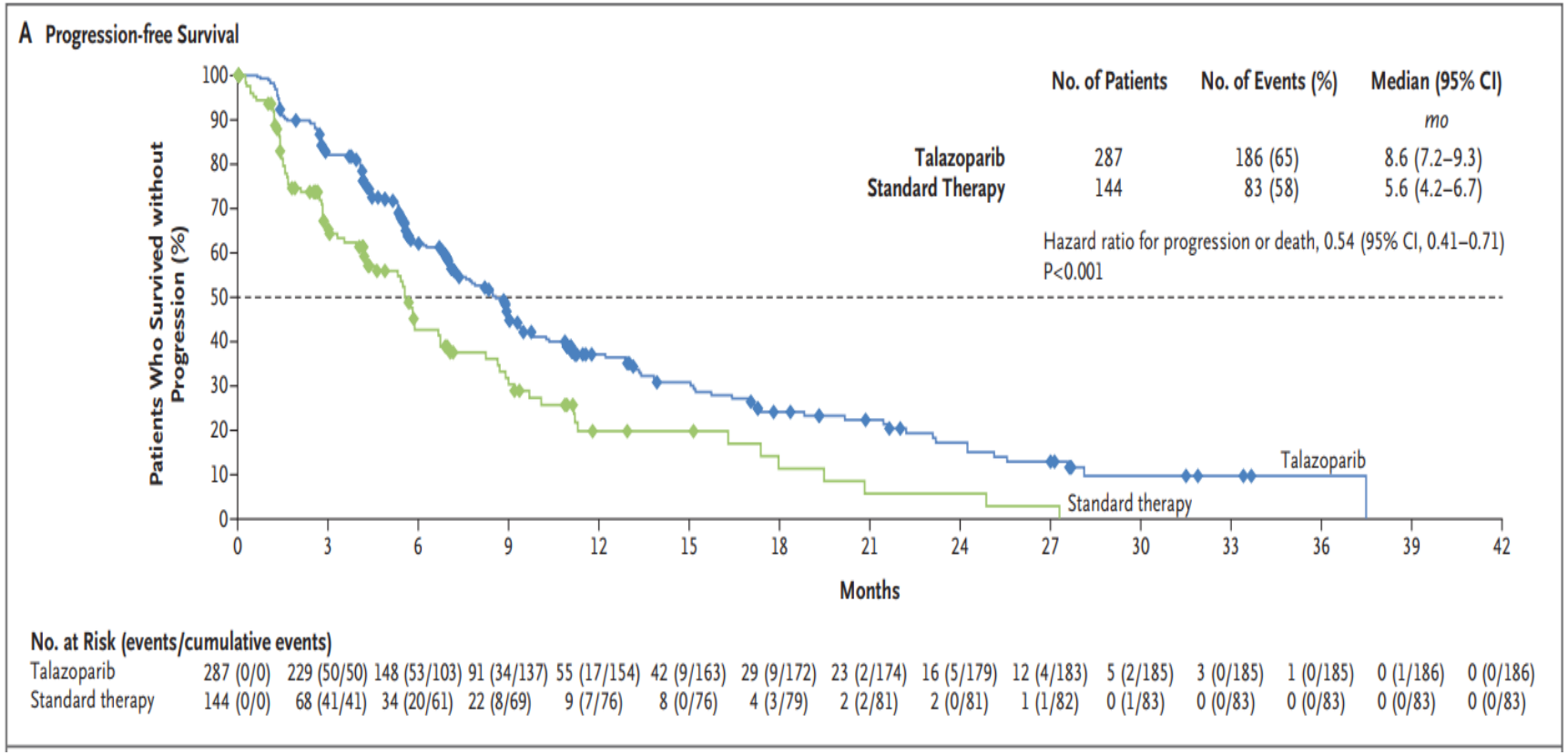


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Talazoparib in Patients with Advanced Breast Cancer and a Germline *BRCA* Mutation

Jennifer K. Litton, M.D., Hope S. Rugo, M.D., Johannes Ettl, M.D., Sara A. Hurvitz, M.D., Anthony Gonçalves, M.D., Ph.D., Kyung-Hun Lee, M.D., Ph.D., Louis Fehrenbacher, M.D., Rinat Yerushalmi, M.D., Lida A. Mina, M.D., Miguel Martin, M.D., Ph.D., Henri Roché, M.D., Ph.D., Young-Hyuck Im, M.D., Ph.D., Ruben G.W. Quek, Ph.D., Denka Markova, Ph.D., Iulia C. Tudor, Ph.D., Alison L. Hannah, M.D., Wolfgang Eiermann, M.D., and Joanne L. Blum, M.D., Ph.D.



NCCN Guidelines® Update: HR+/HER2– MBC

HR+/HER2– MBC and Premenopausal or Postmenopausal Receiving Ovarian Ablation or Suppression

Setting	Preferred Regimens	Other Recommended Regimens (First and Subsequent Lines)
First line	AI + CDK4/6 inhibitor ▪ AI + ribociclib (Category 1) ▪ AI + abemaciclib ▪ AI + palbociclib	Selective ER downregulator ▪ Fulvestrant ▪ Elacestrant for *ESR1*mut tumors Selective ER downregulator (fulvestrant, Category 1) + nonsteroidal AI (anastrozole, letrozole) (Category 1) Nonsteroidal AI ▪ Anastrozole ▪ Letrozole Selective ER modulator ▪ Tamoxifen Steroidal aromatase inactivator ▪ Exemestane
	Fulvestrant + CDK4/6 inhibitor ▪ Fulvestrant + ribociclib (Category 1) ▪ Fulvestrant + abemaciclib (Category 1) ▪ Fulvestrant + palbociclib	
Second line	Fulvestrant + CDK4/6 inhibitor, if CDK4/6 inhibitor not previously used (Category 1)	
	▪ Alpelisib + fulvestrant for *PIK3CA* activating mutations (Category 1) ▪ Capivasertib + fulvestrant for *PIK3CA/AKT1/PTEN* activating mutations (Category 1)	
	Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)	

Conclusions in the treatment of ER+ HER2 low or negative MBC

During the last decade, we have witness an increíble change in the landscape in the treatment of ER+ metastatic breast cancer

The introduction of targeted therapy including CDKi, oral SERDs, PIK3CA/AKTi have impact progression-free survival and overall survival in ER+ metastatic breast cancer

The introduction of antibody drug conjugates (ADCs) have also impact progression-free survival and overall survival in ER+ metastatic breast cancer

The understand of molecular biology of ER+ breast cancer has led to developed new targeted agents that add a step forward to precision medicine.