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Targeted Treatments for HR+, HER2- Metastatic Breast Cancer

Abbreviations:
HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor.

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Objectives

- **Appraise** the non-endocrine targeted therapy treatment options in HR+, HER2- metastatic breast cancer
- **Appreciate** the mechanism of action/pathway profiles of different therapy classes approved for HR+, HER2- metastatic breast cancer
- **Increase expertise** in phase 2/3 clinical studies (Study Design, Efficacy, and Safety Results) utilized to inform the FDA-approved indications of targeted therapies for HR+, HER2- metastatic breast cancer, with no intention of showing any comparison across studies
- **Summarize** the data of Lilly and non-Lilly molecules in a precise and concise manner

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Abbreviations:
FDA=The US Food and Drug Administration; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor.

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Abbreviations:
CDK=Cyclin-Dependent Kinase; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; MBC=Metastatic Breast Cancer; mTOR=Mechanistic Target of Rapamycin; PARP=Poly (ADP-Ribose) Polymerase; PI3K=Phosphoinositide-3-Kinase; SERD=Selective Estrogen Receptor Degrader; SOC=standard of care.

Different Targeted Therapy Classes Approved for HR+, HER2- MBC

CDK 4 & 6 Inhibitors

- **Palbociclib** (Ibrance®)[1]
- **Ribociclib** (Kisqali®)[2]
- **Abemaciclib** (Verzenio®)[3]

Other Targeted Therapies

PI3K/AKT/mTOR Inhibitors

- **Alpelisib** (Piqray®)[4]
- **Capivasertib** (Truqap®)[5]
- **Everolimus** (Afinitor®)[6]

PARP Inhibitors

- **Talazoparib** (Talzenna®)[7]
- **Olaparib** (Lynparza®)[8]

SERMs/SERDs

- **Elacestrant** (Orserdu®)[9]

Abbreviations: CDK=Cyclin-Dependent Kinase; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; MBC=Metastatic Breast Cancer; mTOR=Mechanistic Target of Rapamycin; PARP=Poly (ADP-Ribose) Polymerase; PI3K=Phosphoinositide-3-Kinase; SERDs=Selective Estrogen Receptor Degraders; SERMs=Selective Estrogen Receptor Modulator.

References: 1. Ibrance [US PI]. New York, NY, USA: Pfizer, 2023. https://labeling.pfizer.com/ShowLabeling.aspx?id=12921 (Accessed March 10, 2023). 2. Kisqali [US PI]. East Hanover, NJ, USA: Novartis, 2023. https://www.novartis.us/sites/www.novartis.us/files/kisqali.pdf (Accessed March 10, 2023). 3. Verzenio [US PI]. Indianapolis, IN, USA: Eli Lilly and Company, 2024. https://uspl.lilly.com/verzenio/verzenio.html#pi (Accessed March 10, 2023). 4. Piqray [US PI]. East Hanover, NJ, USA: Novartis, 2022. https://www.novartis.us/sites/www.novartis.us/files/piqray.pdf (Accessed March 10, 2023). 5. Truqap [US PI]. Wilmington, DE, USA: AstraZeneca, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/218197s000lbl.pdf (Accessed March 10, 2023). 6. Afinitor [US PI]. East Hanover, NJ, USA: Novartis, 2022. https://www.novartis.us/sites/www.novartis.us/files/afinitor.pdf (Accessed March 10, 2023). 7. Talzenna [US PI]. New York, NY, USA: Pfizer, 2023. https://labeling.pfizer.com/ShowLabeling.aspx?id=11046 (Accessed March 10, 2023). 8. Lynparza [US PI]. Wilmington, DE, USA: AstraZeneca, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208558s014lbl.pdf (Accessed March 10, 2023). 9. Orserdu [US PI]. New York, NY, USA: Stemline Therapeutics, 2023. https://rxmenarinistemline.com/ORSERDU_elacestrant_Full_Prescribing_Information.pdf (Accessed March 10, 2023).

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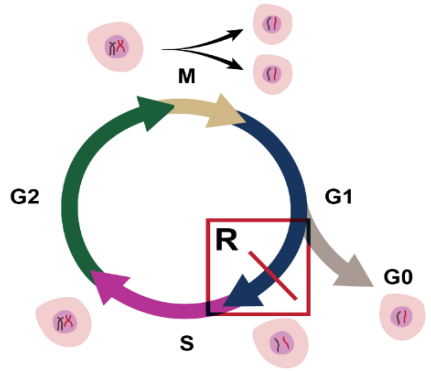
CDK 4 & 6 Inhibitors: An Overview

Abbreviations:
CDK=Cyclin-Dependent Kinase.

CDK 4 & 6: Role in Cancer

Cell Cycle

- Transition from G1 to S phase is a key checkpoint for cell cycle regulation[1]
- Beyond the restriction (R) point, cells become “committed” to the cell cycle and growth factors are no longer required[1,2]

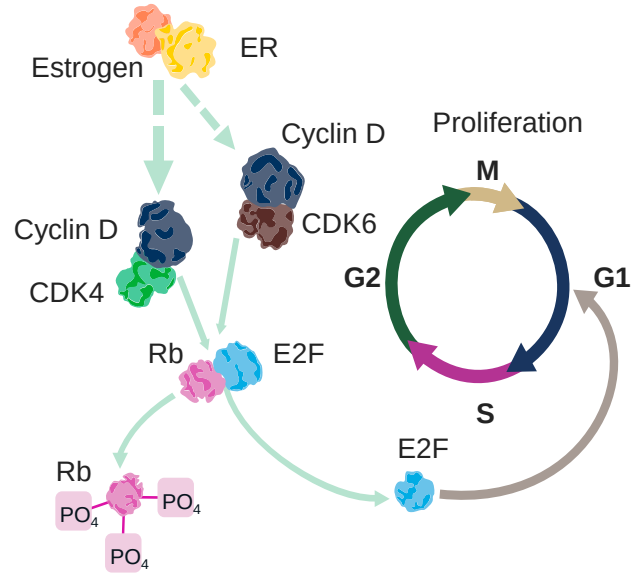


CDKs

CDKs, including CDK 4 & 6, regulate critical checkpoints and play a direct role in cell cycle progression[2]

- The CDK 4 & 6 Rb pathway is estimated to be dysregulated in >80% of human tumors[2-4]
- Excessive CDK 4 & 6 activity may directly contribute to both initiation and maintenance of transformed state by suppressing senescence[5]

Activation of CDK 4 & 6 Leads to Cellular Proliferation[2,6]



Abbreviations: CDK=Cyclin-Dependent Kinase; E2F=E2 Factor; ER=Estrogen Receptor; G1=Gap Phase 1; G2=Gap Phase 2; M=Mitosis; PO_4=Phosphate; Rb=Retinoblastoma; S=Synthesis.

References: 1. Maricarmen D Planas-Silva, Robert A Weinberg. The restriction point and control of cell proliferation. *Current Opinion in Cell Biology*. 1997;9(6):768-772. 2. Sánchez-Martínez C, Gelbert LM, Lallena MJ, de Dios A. Cyclin dependent kinase (CDK) inhibitors as anticancer drugs. *Bioorg Med Chem Lett*. 2015;25(17):3420-3435. 3. Vermeulen K, Van Bockstaele DR, Berneman ZN. The cell cycle: a review of regulation, deregulation and therapeutic targets in cancer. *Cell Prolif*. 2003;36(3):131-149. 4. Ortega S, Malumbres M, Barbacid M. Cyclin D-dependent kinases, INK4 inhibitors and cancer. *Biochim Biophys Acta*. 2002;1602(1):73-87. 5. Torres-Guzmán R, Calsina B, Hermoso A, et al. Preclinical characterization of abemaciclib in hormone receptor positive breast cancer. *Oncotarget*. 2017;8(41):69493-69507. 6. Braal CL, Jongbloed EM, Wilting SM, Mathijssen RHJ, Koolen SLW, Jager A. Inhibiting CDK 4 & 6 in breast cancer with palbociclib, ribociclib, and abemaciclib: similarities and differences. Drugs. 2021;81(3):317-331.

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CDK 4 & 6 Inhibitors: Key Characteristics

Characteristic	Palbociclib[2]	Ribociclib[3]	Abemaciclib[4]
Target[1] (IC_{50}, nM)	CDK4 (11); CDK6 (15)	CDK4 (10); CDK6 (39)	CDK4 (2); CDK6 (10)
Route of administration	Oral	Oral	Oral
Dose, mg	125 QD	600 QD	Monotherapy: 200 BID Combination with ET: 150 BID
Schedule	3 weeks on/1 week off	3 weeks on/1 week off	Continuous
Half-life[2-5], hours	24-34	30-55	17-38

Abbreviations: ; BID=Twice Daily; CDK=Cyclin-Dependent Kinase; ET=Endocrine Therapy; IC_{50}=Half Maximal Inhibitory Concentration; QD=Once Daily.

References: 1. Hamilton E, Infante JR. Targeting CDK4 & 6 in patients with cancer. *Cancer Treat Rev.* 2016;45:129-38. 2. Ibrance [US PI]. New York, NY, USA: Pfizer, 2023. https://labeling.pfizer.com/ShowLabeling.aspx?id=12921 (Accessed March 10, 2023). 3. Kisqali [US PI]. East Hanover, NJ, USA: Novartis, 2021. https://www.novartis.us/sites/www.novartis.us/files/kisqali.pdf (Accessed March 10, 2023). 4. Verzenio [US PI]. Indianapolis, IN, USA: Eli Lilly and Company, 2024. https://uspl.lilly.com/verzenio/verzenio.html#pi (Accessed January 16, 2024). 5. Braal CL, Jongbloed EM, Wilting SM, Mathijssen RHJ, Koolen SLW, Jager A. Inhibiting CDK4 & 6 in Breast Cancer with Palbociclib, Ribociclib, and Abemaciclib: Similarities and Differences. *Drugs*. 2021;81(3):317-331.

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CDK 4 & 6 Inhibitors: Key Clinical Trials

Agent	Combination With AI	Combination With Fulvestrant	Monotherapy
Palbociclib[1-5]	**First line:** • PALOMA-2: letrozole	**First or second line or beyond:** • PALOMA-3: fulvestrant	N/A
Ribociclib[6-9]	**First line:** • MONALEESA-2: letrozole • MONALEESA-7*,[a]: NSAI	**First or second line:** • MONALEESA-3: fulvestrant	N/A
Abemaciclib[10-13]	**First line:** • MONARCH 3: anastrozole or letrozole	**First or second line:** • MONARCH 2: fulvestrant	PD on or after ET and 1-2 CT regimens: • MONARCH 1

*Premenopausal women; NSAI or tamoxifen given in combination with goserelin.
[a]Tamoxifen in combination with ribociclib not indicated due to increased risk for QTc prolongation.

Abbreviations: AI=Aromatase Inhibitor; CDK=Cyclin-Dependent Kinase; CT=Chemotherapy; ET=Endocrine Therapy; FDA=The US Food and Drug Administration; HR=Hormone Receptor; MBC=Metastatic Breast Cancer; N/A=Not Applicable; NSAI=Nonsteroidal Aromatase Inhibitor; PD=Progressive Disease.

References: 1. Palbociclib [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207103s010lbl.pdf (Revised February 2019; Accessed March 10, 2023). 2 Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of estrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol.* 2015;16:25-35. 3. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *NEJM.* 2016;375:1925-1936. 4. Turner NC, Ro J, André F, et al; PALOMA3 Study Group. Palbociclib in hormone-receptor-positive advanced breast cancer. *NEJM.* 2015;373(3):209-219. 5. Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol.* 2016;17:425-439. 6. Ribociclib [package insert]. https://www.novartis.us/sites/www.novartis.us/files/kisqali.pdf (Revised December 2021; Accessed March 10, 2023). 7. Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. *Ann Oncol.* 2018;29:1541-1547. 8. Slamon DJ, Neven P, Chia S, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. *J Clin Oncol.* 2018;36(24):2465-2472. 9. Tripathy D, Im S-A, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *Lancet Oncol.* 2018;19(7):904-915; doi: 10.1016/S1470-2045(18)30292-4.10. Abemaciclib [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208855s000lbl.pdf (Revised February 2018; Accessed March 10, 2023). 11. Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol.* 2017;35:3638-3646. 12. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+, HER2- advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol.* 2017;35:2875-2884. 13. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a phase II study of abemaciclib, a CDK 4 & 6 inhibitor, as a single agent, in patients with refractory HR+, HER2-metastatic breast cancer. *Clin Cancer Res.* 2017;23:5218-5224.

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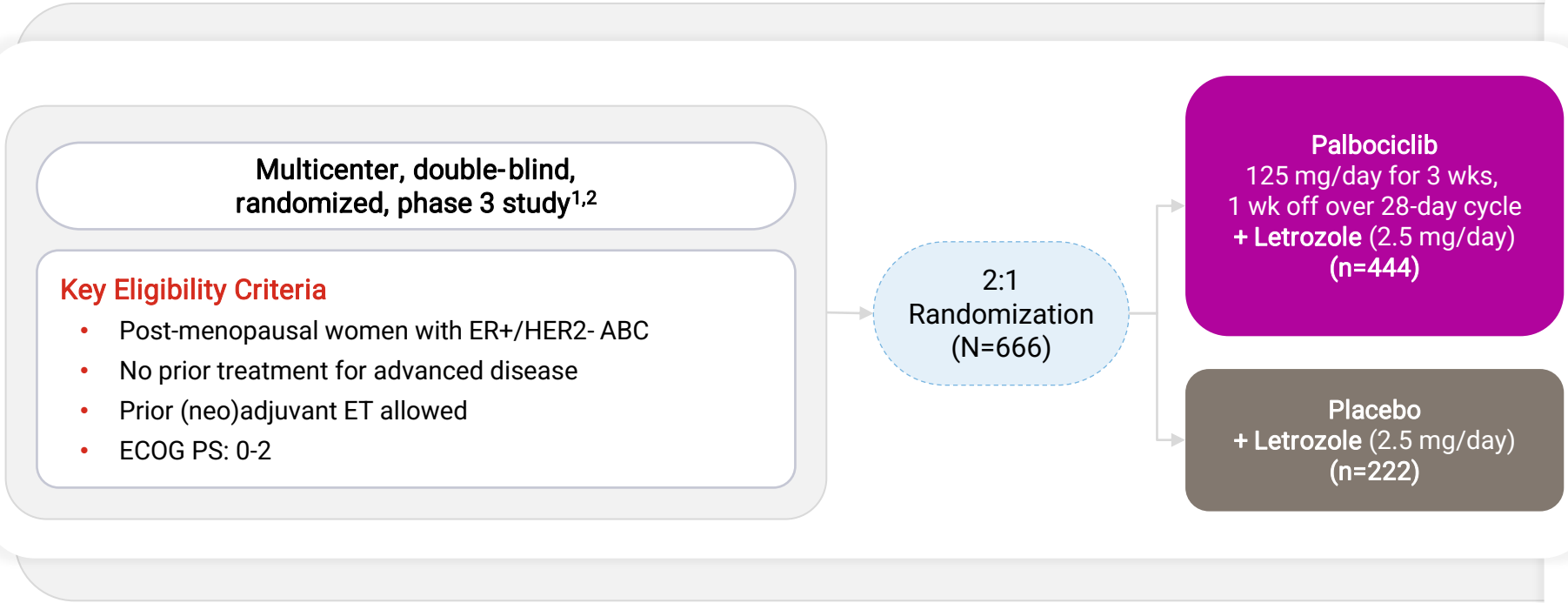
CDK 4 & 6 Inhibitor + Aromatase Inhibitors

- PALOMA-2
- MONALEESA-2
- MONALEESA-7
- MONARCH 3

Abbreviations:
CDK=Cyclin-Dependent Kinase.

PALOMA-2
Study Design



Primary Endpoint
- *Investigator-assessed PFS*

Secondary Endpoints
- *OS, ORR, CBR, DoR, and PROs*
- *Safety and pharmacokinetic effects*
- *Tissue biomarker assessments*

Stratification Factors
- *Disease site (visceral vs. nonvisceral)*
- *Disease-free interval (de novo metastatic; ≤12 vs. >12 mos)*
- *Prior neoadjuvant or adjuvant anticancer therapy (yes vs. no)*

Clinical Trial Identification: NCT01740427
Abbreviations: ABC=Advanced Breast Cancer; CBR=Clinical Benefit Rate; DoR=Duration of Response; ECOG PS=Eastern Cooperative Oncology Group Performance Status; ER=Estrogen Receptor; ET=Endocrine Therapy; HER2=Human Epidermal Growth Factor Receptor 2; Mo=Month; ORR=Objective Response Rate; OS=Overall Survival; PFS=Progression-Free Survival; PRO=Patient-Reported Outcome; Wk=Week.
References: 1. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *NEJM.* 2016;375(20):1925-1936. 2. Finn RS et al. Presented at: ASCO 2016. Abstract 507.

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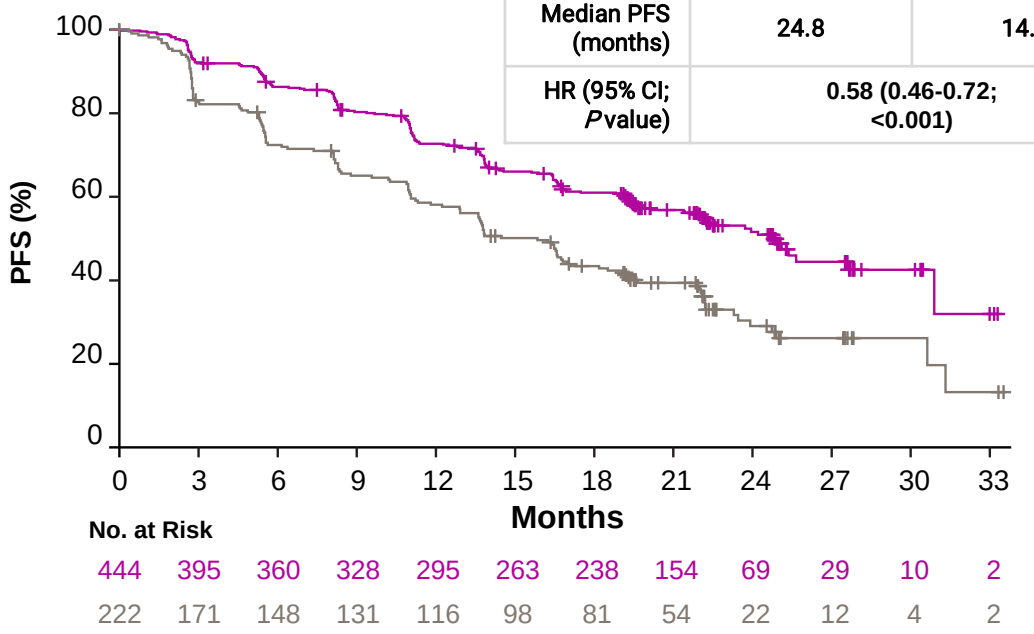
PALOMA-2
Efficacy Results

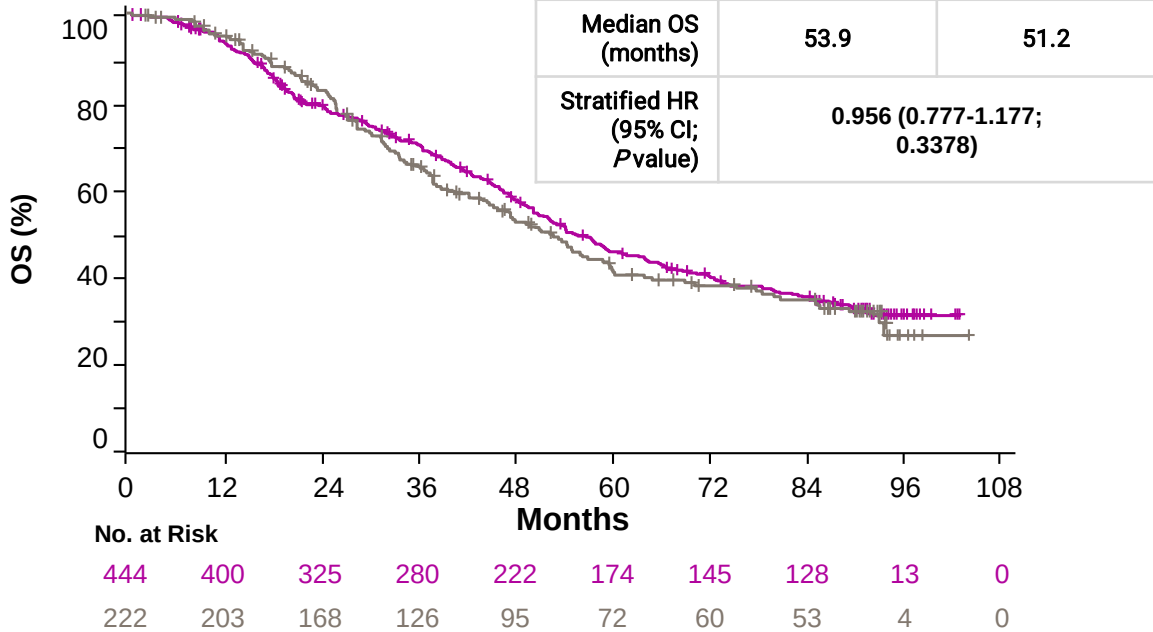
Investigator-Assessed PFS[1a]

	Palbociclib + Letrozole	Placebo + Letrozole
Median PFS (months)	24.8	14.5
HR (95% CI; *P* value)	0.58 (0.46-0.72; <0.001)	



Final Overall Survival[2b]

	Palbociclib + Letrozole	Placebo + Letrozole
Median OS (months)	53.9	51.2
Stratified HR (95% CI; *P* value)	0.956 (0.777-1.177; 0.3378)	



Palbociclib + letrozole demonstrated a significantly longer mPFS than letrozole alone in postmenopausal women with ER+/HER2- ABC, but not an OS benefit

[a]Primary endpoint was met at the final analysis (data cut-off: Nov 29, 2013) Median follow-up: 23 months. [b]Data cut off: Nov 2021. Median follow-up: 90 months.
Clinical Trial Identification: NCT01740427
Abbreviations: ABC=Advanced Breast Cancer; CI=Confidence Interval; ER=Estrogen Receptor; HER=human epidermal growth factor receptor; HR=Hazard Ratio; mPFS=Median PFS; OS=Overall Survival; PFS=Progression-Free Survival.
References: 1. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *NEJM.* 2016;375(20):1925-1936. 2. Finn RS et al. Presented at: ASCO 2022. Abstract LBA1003.

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PALOMA-2
*Safety Results**

AEs ≥20% in either arm, n (%)	Palbociclib + Letrozole (n=444)		Placebo + Letrozole (n=222)^	
	Any Grade	Grade 3 + 4[#]	Any Grade	Grade 3 + 4
Any AEs	439 (98.9)	336 (75.7)	212 (95.5)	54 (24.4)
Neutropenia[a]	353 (79.5)	295 (66.5)	14 (6.3)	3 (1.4)
Leukopenia[b]	173 (39.0)	110 (24.8)	5 (2.3)	0
Fatigue	166 (37.4)	8 (1.8)	61 (27.5)	1 (0.5)
Nausea	156 (35.1)	1 (0.2)	58 (26.1)	4 (1.8)
Arthralgia	148 (33.3)	3 (0.7)	75 (33.8)	1 (0.5)
Alopecia[c]	146 (32.9)	0	35 (15.8)	0
Diarrhea	116 (26.1)	6 (1.4)	43 (19.4)	3 (1.4)
Cough	111 (25.0)	0	42 (18.9)	0
Anemia[d]	107 (24.1)	24 (5.4)	20 (9.0)	4 (1.8)
Back pain	96 (21.6)	6 (1.4)	48 (21.6)	0
Headache	95 (21.4)	1 (0.2)	58 (26.1)	4 (1.8)
Hot flush	93 (20.9)	0	68 (30.6)	0

Warnings & Precautions

Palbociclib can cause Neutropenia, Interstitial Lung Disease/Pneumonitis and Embryo- Fetal Toxicity. For more information, please see full US prescribing information at https://labeling.pfizer.com/ShowLabeling.aspx?id=2191.

In the palbociclib + letrozole arm, neutropenia, leukopenia, fatigue, nausea, and arthralgia were the most common any grade AEs

*Data cut-off: Safety analysis – February 26, 2016 (final analysis).
Clinical Trial Identification: NCT01740427.
Safety analysis: Data cut-off – February 26, 2016 (primary analysis) AEs were characterized and graded according to MedDRA.
[a]Neutropenia and neutrophil count decreased. [b]Leukopenia and white blood cell count decreased. [c]Palbociclib + letrozole: 30.2% of the patients had grade 1 and 2.7% had grade 2 alopecia; placebo + letrozole: 14.9% of patients had grade 1 and 0.9% had grade 2 alopecia. [d]Anemia, hematocrit decreased, and hemoglobin decreased.
[#]Grade 4 events (not shown): increased alanine aminotransferase level, increased blood creatinine level, febrile neutropenia, pulmonary embolism, acute kidney injury, hyperuricemia, acute pancreatitis, pathologic fracture, pericardial effusion, sepsis, increased amylase level, aortic valve stenosis, pulmonary edema, staphylococcal bacteremia, thrombotic cerebral infarction, urosepsis, and increased lipase level; these grade 4 events were reported in 1 patient each, except for increased lipase level, which was reported in 2 patients. ^One death secondary to lower respiratory tract infection and pulmonary embolism occurred in the placebo + letrozole group (treatment related).
Abbreviations: AE=Adverse Event; MedDRA=Medical Dictionary for Regulatory Activities.
Reference: Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *NEJM.* 2016;375(20):1925-1936; doi: 10.1056/NEJMoa1607303.

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MONALEESA-2
Study Design

Multicenter, double-blind, randomized, phase 3 study[1,2]

Key Eligibility Criteria

- Post-menopausal women with HR+, HER2- recurrent or MBC
- No prior treatment for advanced disease
- Prior (neo)adjuvant ET allowed
- ECOG PS: 0 or 1

1:1 Randomization (N=668)

Ribociclib 600 mg/day for 3 wks, 1 wk off over 28-day cycle **+ Letrozole** (2.5 mg/day) **(n=334)**

Placebo + Letrozole (2.5 mg/day) **(n=334)**

Primary Endpoint

- *Investigator-assessed PFS*

Secondary Endpoints

- *OS, ORR, and CBR*
- *Safety and QoL*

Stratification Factors

- *Presence or absence of liver and/or lung metastases*

Clinical Trial Identification: NCT01958021.
Abbreviations: CBR=Clinical Benefit Rate; ECOG PS=Eastern Cooperative Oncology Group Performance Status; ET=Endocrine Therapy; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; MBC=Metastatic Breast Cancer; ORR=Objective Response Rate; OS=Overall Survival; PFS=Progression-Free Survival; QoL=Quality of Life; Wk=Week.
References: 1. Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. *Ann Oncol.* 2018;29(7):1541-1547. 2. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *NEJM.* 2016;375(18):1738-1748. Erratum in: *NEJM.* 2018;379(26):2582.

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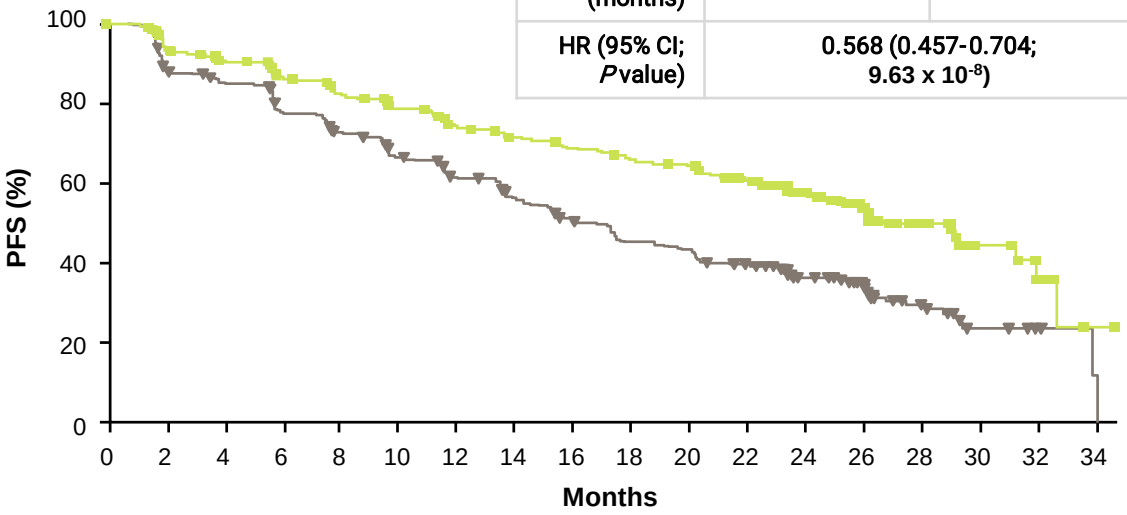
MONALEESA-2
Efficacy Results

Investigator-Assessed PFS[a] (Updated Analysis)[1]

	Ribociclib + Letrozole	Placebo + Letrozole
Median PFS (months)	25.3	16.0
HR (95% CI; *P* value)	0.568 (0.457-0.704; 9.63×10^{-8})	

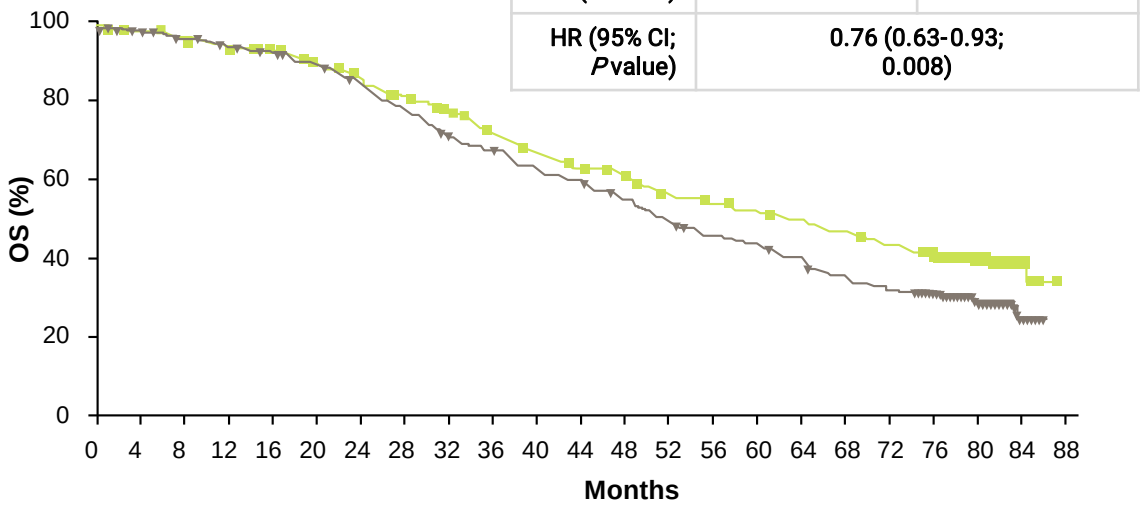


No. at Risk

334	294	277	257	240	227	207	196	188	176	164	132	97	46	17	11	1	0
334	279	265	239	219	196	179	156	138	124	110	93	63	34	10	7	2	0

OS Benefit[2b]

	Ribociclib + Letrozole	Placebo + Letrozole
Median OS (months)	63.9	51.4
HR (95% CI; *P* value)	0.76 (0.63-0.93; 0.008)	



No. at Risk

334	323	315	305	300	284	270	253	237	220	202	191	180	165	158	150	142	135	125	101	48	8	0
334	326	316	305	306	293	283	244	222	209	195	183	167	149	139	131	114	104	94	73	38	6	0

Ribociclib + letrozole demonstrated a significantly longer mOS and mPFS than letrozole alone in postmenopausal women with HR+, HER2- ABC or MBC

[a]Data cut-off: January 2, 2017. Median duration of follow-up: 26.4 months. [b]Data cut-off: June 10, 2021. Median duration of follow-up: 80 months.

Clinical Trial Identification: NCT01958021

Abbreviations: ABC=Advanced Breast Cancer; CI=Confidence Interval; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; HR=Hazard Ratio; MBC=Metastatic Breast Cancer; mOS - Median Overall Survival; mPFS=Median Progression-Free Survival.

References: 1. Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. Ann Oncol. 2018;29(7):1541-1547. 2. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer. NEJM. 2022; 386:942-950.

MONALEESA-2

Safety Results (1/2)*

AEs ≥20 % in either arm, n (%)	Ribociclib + Letrozole (n=334)		Placebo + Letrozole^ (n=330)	
	Any Grade	Grade 3 + 4[#]	Any Grade	Grade 3 + 4
Neutropenia[a]	257 (76.9)	207 (62.0)	19 (5.8)	4 (1.2)
Nausea	178 (53.3)	8 (2.4)	101 (30.6)	2 (0.6)
Fatigue	138 (41.3)	10 (3.0)	107 (32.4)	3 (0.9)
Diarrhea	128 (38.3)	8 (2.4)	81 (24.5)	3 (0.9)
Alopecia	115 (34.4)	0	53 (16.1)	0
Vomiting	112 (33.5)	12 (3.6)	55 (16.7)	3 (0.9)
Arthralgia	111 (33.2)	3 (0.9)	108 (32.7)	4 (1.2)
Leukopenia[b]	110 (32.9)	71 (21.3)	15 (4.5)	3 (0.9)
Constipation	93 (27.8)	4 (1.2)	71 (21.5)	0
Headache	90 (26.9)	1 (0.3)	69 (20.9)	2 (0.6)
Hot flash	82 (24.6)	1 (0.3)	84 (25.5)	0
Back pain	81 (24.3)	10 (3.0)	67 (20.3)	1 (0.3)
Cough	77 (23.1)	0	70 (21.2)	0
Rash[c]	74 (22.2)	5 (1.5)	29 (8.8)	0
Anemia[d]	71 (21.3)	8 (2.4)	19 (5.8)	4 (1.2)

*Data cut-off: Safety analysis – January 4, 2017.
Clinical Trial Identification: NCT01740427
Safety analysis: Data cut-off – February 26, 2016 (primary analysis) AEs were characterized and graded according to MedDRA.
[a]Neutropenia and neutrophil count decreased. [b]Leukopenia and white blood cell count decreased. [c]Palbociclib + letrozole: 30.2% of the patients had grade 1 and 2.7% had grade 2 alopecia; placebo + letrozole: 14.9% of patients had grade 1 and 0.9% had grade 2 alopecia.[d]Anemia, hematocrit decreased, and hemoglobin decreased.
[#]Grade 4 events (not shown): increased alanine aminotransferase level, increased blood creatinine level, febrile neutropenia, pulmonary embolism, acute kidney injury, hyperuricemia, acute pancreatitis, pathologic fracture, pericardial effusion, sepsis, increased amylase level, aortic valve stenosis, pulmonary edema, staphylococcal bacteremia, thrombotic cerebral infarction, urosepsis, and increased lipase level; these grade 4 events were reported in 1 patient each, except for increased lipase level, which was reported in 2 patients. ^One death secondary to lower respiratory tract infection and pulmonary embolism occurred in the placebo + letrozole group (treatment related).
Abbreviations: AE=Adverse Event; MedDRA=Medical Dictionary for Regulatory Activities.
Reference: Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. *Ann Oncol.* 2018;29(7):1541-1547.

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MONALEESA-2
Safety Results (2/2)*

AEs ≥20 % in either arm, n (%)	Ribociclib + Letrozole (n=334)		Placebo + Letrozole^ (n=330)	
	Any Grade	Grade 3 + 4[#]	Any Grade	Grade 3 + 4
Decreased appetite	69 (20.7)	5 (1.5)	52 (15.8)	1 (0.3)
Abnormal LFTs[e]	67 (20.1)	34 (10.2)	21 (6.4)	8 (2.4)

Warnings & Precautions

Ribociclib can cause Interstitial Lung Disease/Pneumonitis, Severe Cutaneous Adverse Reactions, QT Interval Prolongation, Hepatobiliary Toxicity, Neutropenia, and Embryo-Fetal Toxicity. For more information, please see full US prescribing information at https://www.novartis.us/sites/www.novartis.us/files/kisqali.pdf.

In the ribociclib + letrozole arm, neutropenia, nausea, fatigue, diarrhea and alopecia were the most common any grade AEs

*Data cut-off: Safety analysis – January 4, 2017.
Clinical Trial Identification: NCT01740427
Safety analysis: Data cut-off – February 26, 2016 (primary analysis) AEs were characterized and graded according to MedDRA.
[e]Platelet count decreased and thrombocytopenia.
[#]Grade 4 events (not shown): increased alanine aminotransferase level, increased blood creatinine level, febrile neutropenia, pulmonary embolism, acute kidney injury, hyperuricemia, acute pancreatitis, pathologic fracture, pericardial effusion, sepsis, increased amylase level, aortic valve stenosis, pulmonary edema, staphylococcal bacteremia, thrombotic cerebral infarction, urosepsis, and increased lipase level; these grade 4 events were reported in 1 patient each, except for increased lipase level, which was reported in 2 patients. ^One death secondary to lower respiratory tract infection and pulmonary embolism occurred in the placebo + letrozole group (treatment related).
Abbreviations: AE=Adverse Event; MedDRA=Medical Dictionary for Regulatory Activities.
Reference: Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. *Ann Oncol.* 2018;29(7):1541-1547.

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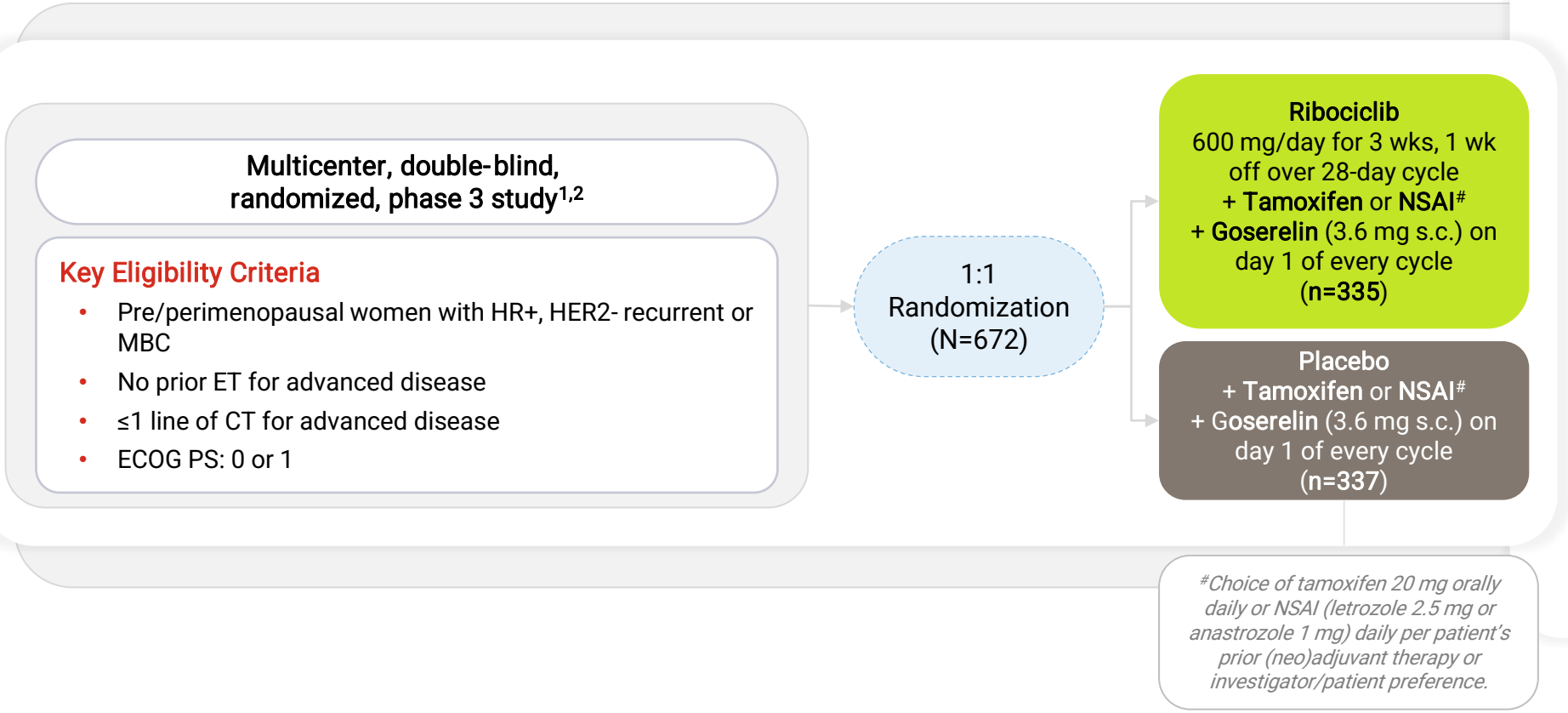
MONALEESA-7
Study Design



Primary Endpoint
- *Investigator-assessed PFS*

Secondary Endpoints
- *OS, ORR, CBR, TTR, DoR, TTDD, and safety*

Stratification Factors
- *Liver or lung metastases (yes vs. no)*
- *Prior CT for advanced disease (yes vs. no)*
- *Endocrine combination partner (tamoxifen vs. NSAI)*

#Choice of tamoxifen 20 mg orally daily or NSAI (letrozole 2.5 mg or anastrozole 1 mg) daily per patient's prior (neo)adjuvant therapy or investigator/patient preference.
Clinical Trial Identification: NCT02278120
Abbreviations: CBR=Clinical Benefit Rate; CT=Chemotherapy; DoR=Duration of Response; ECOG PS=Eastern Cooperative Oncology Group Performance Status; ET=Endocrine Therapy; HR=Hormone Receptor; HER2=Human Epidermal Growth Factor Receptor 2; MBC=Metastatic Breast Cancer; NSAI=Non-steroidal Aromatase Inhibitor; ORR=Objective Response Rate; OS=Overall Survival; PFS=Progression-Free Survival; s.c.=Subcutaneous; TTR=Time to Response; TTDD=Time to Definitive Deterioration; Wk=Week.
References: 1.Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *Lancet Oncol.* 2018;19(7):904-915. 2. Im SA, Lu YS, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *NEJM.* 2019;381(4):307-316.

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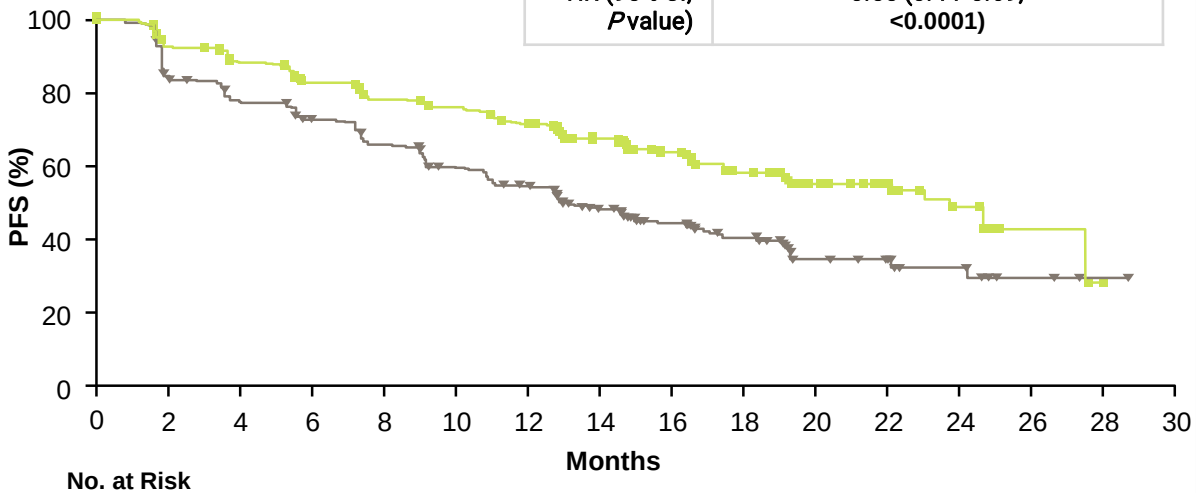
MONALEESA-7
Efficacy Results

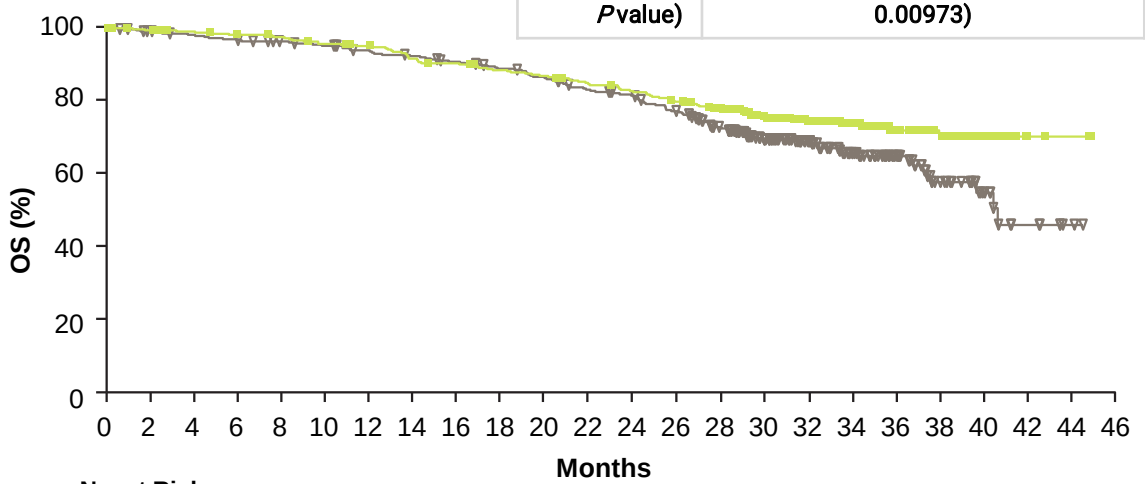
Investigator-Assessed PFS Primary Analysis[1]*

	Ribociclib + ET	Placebo + ET
Median PFS (months)	23.8	13.0
HR (95% CI; *P* value)	0.55 (0.44-0.69; <0.0001)	



OS (Prespecified Interim Analysis)[2†]

	Ribociclib + ET	Placebo + ET
Median OS (months)	NE	40.9
HR (95% CI; *P* value)	0.71 (0.54-0.95; 0.00973)	



Ribociclib + ET demonstrated significantly longer mPFS and mOS than ET alone in pre/perimenopausal women with HR+, HER2- ABC or MBC

*Primary endpoint was met at the primary analysis (Data cut-off: August 20, 2017). †Prespecified interim OS analysis – November 30, 2018.

Clinical Trial Identification: NCT02278120

Abbreviations: ABC=Advanced Breast Cancer; CI=Confidence Interval; ET=Endocrine Therapy; HR=Hormone Receptor; HR=Hazard Ratio; HER2=Human Epidermal Growth Factor Receptor; MBC=Metastatic Breast Cancer; NE=Not Evaluable; OS=Overall Survival; mPFS=Median Progression-Free Survival.

References: 1. Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *Lancet Oncol.* 2018;19(7):904-915. 2. Im SA, Lu YS, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *NEJM.* 2019;381(4):307-316.

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MONALEESA-7
*Safety Results**

AEs ≥20% in either arm, n (%)	Ribociclib + ET (n=335)		Placebo + ET (n=337)	
	Any Grade	Grade 3 + 4	Any Grade	Grade 3 + 4
Any AEs	329 (98)	257 (77)	317 (94)	100 (30)
Neutropenia[a]	254 (76)	203 (61)	26 (8)	12 (4)
Hot flush	114 (34)	1 (<1)	113 (34)	0
Nausea	106 (32)	2 (1)	66 (20)	1 (<1)
Leukopenia	105 (31)	48 (14)	19 (5)	4 (1)
Arthralgia	100 (30)	3 (1)	92 (27)	3 (1)
Fatigue	79 (23)	4 (1)	83 (25)	0
Headache	77 (23)	0	82 (24)	3 (1)
Anemia[b]	70 (21)	10 (3)	34 (10)	7 (2)
Diarrhea	68 (20)	5 (1)	63 (19)	1 (<1)

Warnings & Precautions

Ribociclib can cause Interstitial Lung Disease/Pneumonitis, Severe Cutaneous Adverse Reactions, QT Interval Prolongation, Hepatobiliary Toxicity, Neutropenia, and Embryo-Fetal Toxicity. For more information, please see full US prescribing information at https://www.novartis.us/sites/www.novartis.us/files/kisqali.pdf.

In the ribociclib + ET arm, neutropenia, hot flush, nausea, leukopenia and arthralgia were the most common any grade AEs

*Data cut-off: Safety analysis – August 20, 2017.
Clinical Trial Identification: NCT02278120
Abbreviations: AE=Adverse Event; ET=Endocrine Therapy; LLN=Lower Limit of Normal; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.
Reference: Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *Lancet Oncol.* 2018;19(7):904-915.

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MONARCH 3
Study Design

Multicenter, double-blind, randomized, placebo-controlled, phase 3 study[1,2]

Key Eligibility Criteria

- Postmenopausal women with HR+, HER2- ABC
- No prior systemic therapy in this setting
- If neoadjuvant or adjuvant ET administered, a disease-free interval of >12 months from the completion of ET
- ECOG PS: 0 or 1

2:1 Randomization (N=493)

Abemaciclib 150 mg BID (continuous schedule) + **Anastrozole** (1 mg/day) or^ **Letrozole** (2.5 mg/day) **(n=328)**

Placebo BID (continuous schedule) + **Anastrozole** (1 mg/day) or^ **Letrozole** (2.5 mg/day) **(n=165)**

Primary Endpoint

- *Investigator-assessed PFS*

Secondary Endpoints

- *OS, ORR, DoR, CBR, QoL, safety, and tolerability*

Exploratory Endpoint

- *Chemotherapy-free survival*

Stratification Factors

- *Metastatic site (visceral, bone only, or other)*
- *Prior neoadjuvant or adjuvant ET (AI, no ET, or other)*

Clinical Trial Identification: NCT02246621
Additional Note: NSAI=Anastrozole or Letrozole
Abbreviations: ABC=Advanced Breast Cancer; AI=Aromatase Inhibitor; BID=Twice Daily; CBR=Clinical Benefit Rate; DoR=Duration of Response; ECOG PS=Eastern Cooperative Oncology Group Performance Status; ET=Endocrine Therapy; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; NSAI=Non-steroidal Aromatase Inhibitor; ORR=Objective Response Rate; OS=Overall Survival; PD=Progressive Disease; PFS=Progression-Free Survival; QoL=Quality of Life.

References: 1. Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol.* 2017;35(32):3638-3646. 2. Johnston S, Martin M, Di Leo A, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. *NPJ Breast Cancer.* 2019;5:5.

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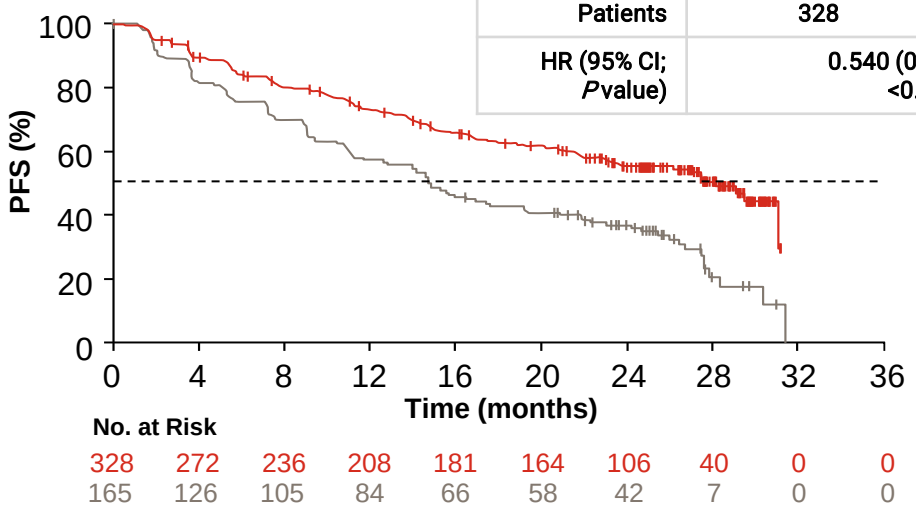
MONARCH 3

Efficacy Results – PFS in the ITT Population

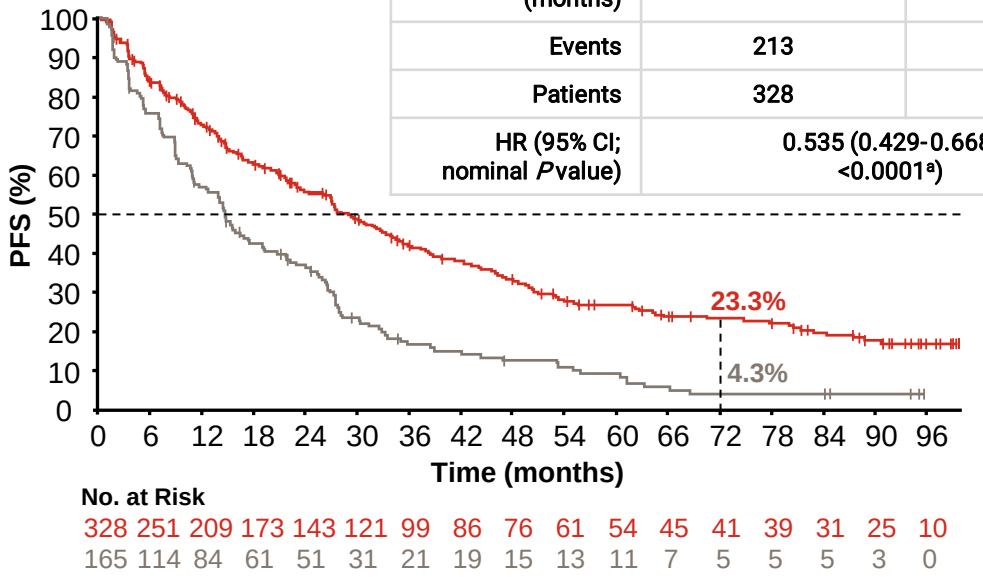
Investigator-Assessed Final PFS[1a]

	Abemaciclib + NSAI	Placebo + NSAI
Median PFS, (months)	28.2	14.8
Events	138	108
Patients	328	165
HR (95% CI; *P*value)	0.540 (0.418-0.698; <0.0001)	



Updated PFS[2b]

	Abemaciclib + NSAI	Placebo + NSAI
Median PFS, (months)	29.0	14.8
Events	213	137
Patients	328	165
HR (95% CI; nominal *P*value)	0.535 (0.429-0.668; <0.0001[a])	



The addition of abemaciclib to NSAI resulted in a 14.3-month improvement in median PFS with continued separation of the curves at longer follow-up.

[a]Primary endpoint was met at the preplanned interim analysis with a data cutoff of January 31, 2017. Final PFS analysis data cutoff was November 3, 2017. [b]Data Cutoff: September 29, 2023.

Clinical Trial Identification: NCT02246621

Abbreviations: ABC=Advanced Breast Cancer; CI=Confidence Interval; ET=Endocrine Therapy; HR=Hormone Receptor; HR=Hazard Ratio; HER2=Human Epidermal Growth Factor Receptor; ITT=intent-to-treat; mPFS=Median PFS; NSAI=Non-steroidal Aromatase Inhibitor. PFS=progression-free survival.

Reference: 1. Verzenio [package insert]. Indianapolis, IN: Eli Lilly and Company; 2024. https://uspl.lilly.com/verzenio/verzenio.html#pi 2. Goetz MP, Masakazu T, Huober J, et al. MONARCH 3: Final overall survival results of abemaciclib plus a nonsteroidal aromatase inhibitor as first line therapy for HR+, HER2 advanced breast cancer. Presented at: SABCS 2023. Abstract GS01-12.

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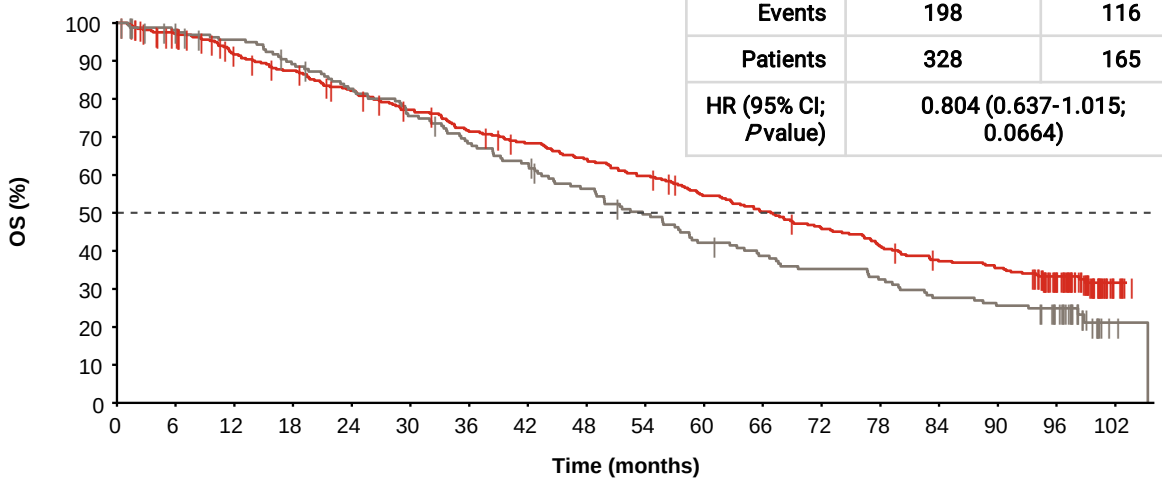
MONARCH 3

Efficacy Results – Overall Survival*

Overall Survival ITT Population

	Abemaciclib + NSAI	Placebo + NSAI
Median, (months)	66.8	53.7
Events	198	116
Patients	328	165
HR (95% CI; *P* value)	0.804 (0.637-1.015; 0.0664)	

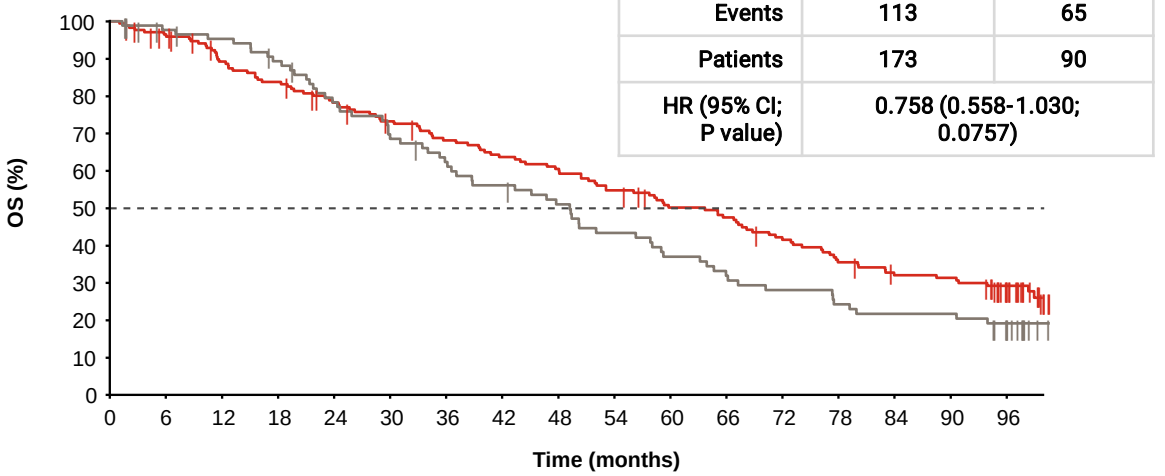


No. at risk

328	304	281	266	247	229	211	199	187	174	156	144	131	117	104	99	66	6
165	155	149	138	127	116	104	95	84	73	62	56	51	47	40	37	28	1

Overall Survival Visceral Population

	Abemaciclib + NSAI	Placebo + NSAI
Median, (months)	63.7	48.8
Events	113	65
Patients	173	90
HR (95% CI; P value)	0.758 (0.558-1.030; 0.0757)	



No. at risk

173	161	147	138	126	116	107	100	95	86	76	72	63	53	46	45	27	3
90	83	80	74	64	56	49	44	40	34	29	24	22	19	17	16	9	0

Abemaciclib in combination with a NSAI resulted in longer OS compared to NSAI alone in both the ITT population and the subgroup with visceral disease (sVD); however, statistical significance was not reached. The observed improvement in median OS was 13.1 months in the ITT population and 14.9 months in the sVD population.

*Data Cutoff: September 29, 2023.

Clinical Trial Identification: NCT02246621

Abbreviations: CI=Confidence Interval; HR=Hazard Ratio; ITT=Intent-to-Treat Analysis; NSAI=Non-steroidal Aromatase Inhibitor; OS=Overall Survival

Reference: Goetz MP, Masakazu T, Huober J, et al. MONARCH 3: Final overall survival results of abemaciclib plus a nonsteroidal aromatase inhibitor as first line therapy for HR+, HER2 advanced breast cancer. Presented at: SABCS 2023. Abstract GS01-12.

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MONARCH 3
*Safety Results**

AEs ≥20% in either arm, n (%)	Abemaciclib + NSAI (n=327)		Placebo + NSAI (n=161)	
	Any Grade	Grade 3 + 4	Any Grade	Grade 3 + 4
Any AEs	323 (98.8)	191 (58.4)	152 (94.4)	40 (24.9)
Diarrhea	269 (82.3)	31 (9.5)	52 (32.3)	2 (1.2)
Neutropenia[a]	143 (43.7)	78 (23.8)	3 (1.9)	2 (1.2)
Fatigue	135 (41.3)	6 (1.8)	54 (33.5)	0
Nausea	135 (41.3)	4 (1.2)	33 (20.5)	2 (1.2)
Anemia[b]	103 (31.5)	23 (7.0)	13 (8.1)	2 (1.2)
Abdominal pain	102 (31.2)	6 (1.8)	21 (13.0)	2 (1.2)
Vomiting	99 (30.3)	5 (1.5)	21 (13.0)	4 (2.5)
Alopecia	90 (27.5)	-	18 (11.2)	-
Decreased appetite	86 (26.3)	5 (1.5)	17 (10.6)	1 (0.6)
Leukopenia	72 (22.0)	28 (8.6)	4 (2.5)	1 (0.6)
Blood creatinine increased	67 (20.5)	7 (2.1)	7 (4.3)	0

Warnings & Precautions

Abemaciclib can cause Diarrhea, Neutropenia, Interstitial Lung Disease/Pneumonitis, Hepatoxicity, Venous Thromboembolism, and Embryo-Fetal Toxicity. For more information, please see full US prescribing information https://uspl.lilly.com/verzenio/verzenio.html#pi.

In the abemaciclib + NSAI arm, diarrhea, neutropenia, fatigue, nausea and anemia were the most common any grade AEs

*Data cut-off: Final PFS analysis – November 3, 2017. [a]Neutropenia, febrile neutropenia, or a decreased neutrophil count. [b]Anemia or a decreased hemoglobin concentration.
Clinical Trial Identification: NCT02246621
Safety analysis: Data cut-off – August 20, 2017 (primary analysis) AEs were characterized and graded according to NCI-CTCAE – Grade 1: (<LLN -1.5 x 10^9/L), Grade 2: (<1.5 to 1.0 x 10^9/L), Grade 3: (<1.0 to 0.5 x 10^9/L), Grade 4: (<0.5 x 10^9/L).
Abbreviations: AE=Adverse Event; ET=Endocrine Therapy; LLN=Lower Limit of Normal; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; NSAI=Non-steroidal Aromatase Inhibitor.
Reference: Verzenio [package insert]. Indianapolis, IN: Eli Lilly and Company; 2024. https://uspl.lilly.com/verzenio/verzenio.html#pi

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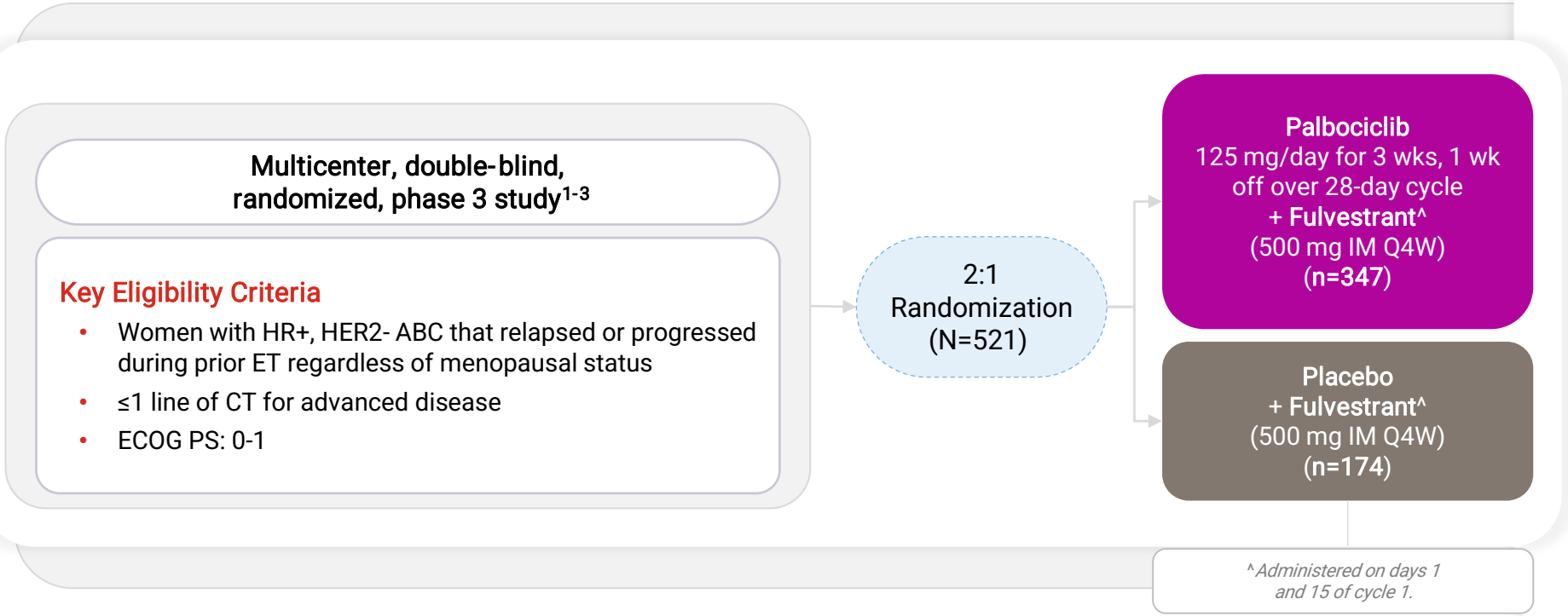
CDK 4 & 6 Inhibitor + Fulvestrant

- PALOMA-3
- MONALEESA-3
- MONARCH 2

Abbreviations:
CDK=Cyclin-Dependent Kinase.

PALOMA-3
Study Design



Primary Endpoint
- *Investigator-assessed PFS*

Secondary Endpoints
- *OS, CBR, ORR, PROs, safety*

Stratification Factors
- *Presence or absence of visceral metastases*
- *Pre-/peri- vs. post-menopausal*
- *Sensitivity to prior ET therapy*

[a]Pre/perimenopausal participants received goserelin for duration of study therapy, starting ≥4 weeks prerandomization and continuing Q28D.
Clinical Trial Identification: NCT01942135
Abbreviations: ABC=Advanced Breast Cancer; CBR=Clinical Benefit Rate; CT=Chemotherapy; ECOG PS=Eastern Cooperative Oncology Group Performance Status; ET=Endocrine Therapy; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; IM=Intramuscular; ORR=Objective Response Rate; OS=Overall Survival; PFS=Progression-Free Survival; PRO=Patient-Reported Outcome; Q4W=Every 4 Weeks; Q28D=Every 28 Days; Wk=Week.
References: 1. Turner NC, Ro J, André F, et al; PALOMA3 Study Group. Palbociclib in hormone-receptor-positive advanced breast cancer. *NEJM.* 2015;373(3):209-219. 2. Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol.* 2016;17(4):425-439. 3. Cristofanilli M et al. Presented at: ASCO 2021. Abstract 1000.

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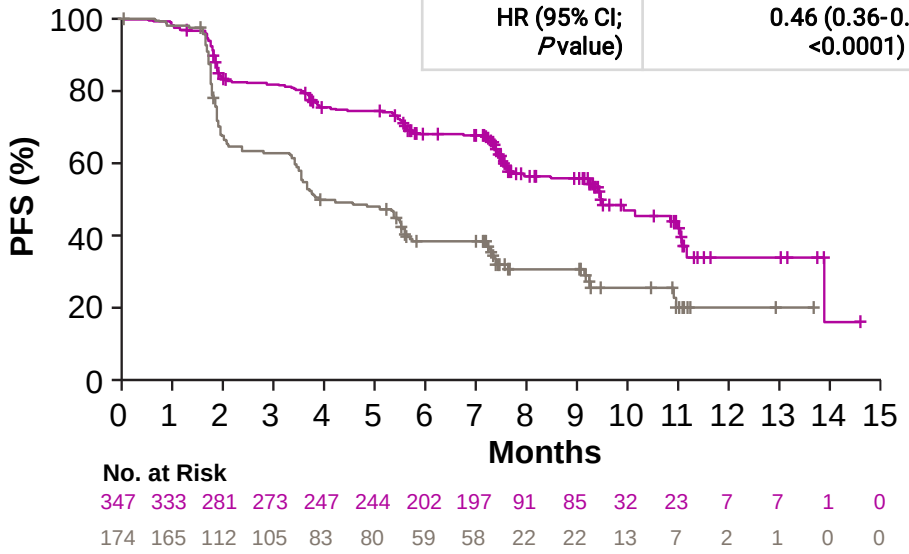
PALOMA-3
*Efficacy Results**

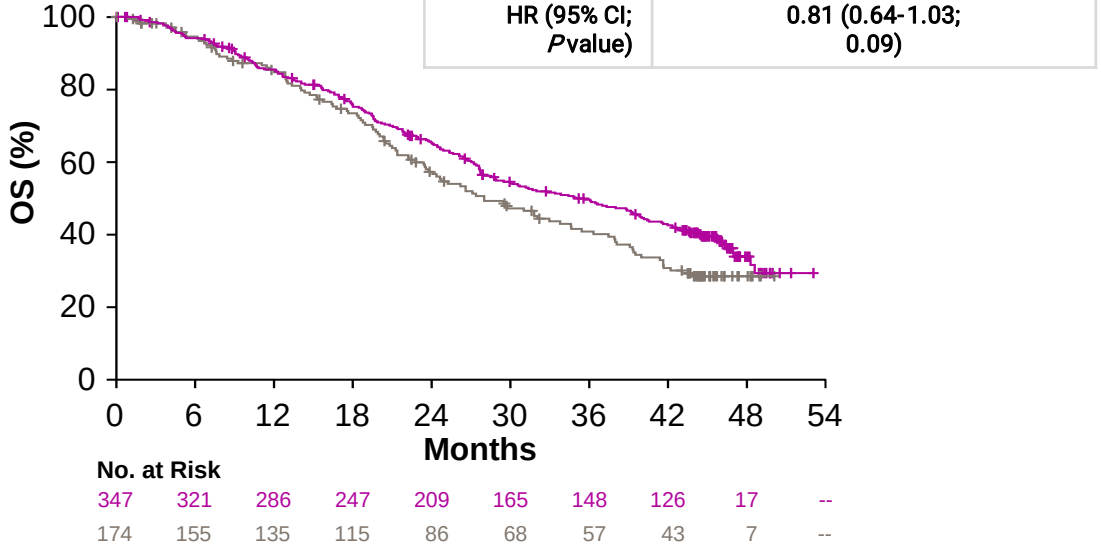
Investigator-Assessed Final PFS[1a]

	Palbociclib + Fulvestrant	Placebo + Fulvestrant
Median PFS (months)	9.5	4.6
HR (95% CI; *P* value)	0.46 (0.36-0.59; <0.0001)	



OS[2]

	Palbociclib + Fulvestrant	Placebo + Fulvestrant
Median OS (months)	34.9	28.0
HR (95% CI; *P* value)	0.81 (0.64-1.03; 0.09)	



Palbociclib + fulvestrant demonstrated a significantly longer mPFS and numerically longer mOS than fulvestrant alone in patients with HR+/HER2- ABC who had progressed on prior ET

*Data cut-off: Interim analysis – December 05, 2014; final PFS analysis – March 16, 2015; updated OS analysis – April 13, 2018.
[a]Primary endpoint was met at the interim analysis (data cut-off: December 05, 2014).
Clinical Trial Identification: NCT01942135
Abbreviations: ABC=Advanced Breast Cancer; CI=Confidence Interval; ET=Endocrine Therapy; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; HR=Hazard Ratio; mOS=MedianOverall Survival; mPFS=Median Progression-Free Survival.
References: 1. Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol.* 2016;17(4):425-439. 2. Turner NC, Slamon DJ, Ro J, et al: Overall survival with palbociclib and fulvestrant in advanced breast cancer. *NEJM.* 379:1926-1936, 2018.

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PALOMA-3
*Safety Results**

AEs ≥20 % in either arm, n (%)	Palbociclib + Fulvestrant (n=345)		Placebo + Fulvestrant (n=172)	
	Any Grade	Grade 3 + 4	Any Grade	Grade 3 + 4
Neutropenia	279 (81)	223 (65)	6 (4)	1 (1)
Anemia	96 (28)	10 (3)	19 (11)	3 (2)
Leukopenia	171 (50)	95 (28)	7 (5)	2 (2)
Infections	144 (<43)	7 (<3)	52 (30)	5 (3)
Fatigue	135 (39)	8 (2)	49 (28)	2 (1)
Nausea	112 (32)	0	47 (28)	1 (1)
Headache	80 (24)	2 (1)	33 (19)	0
Diarrhea	74 (21)	0	32 (19)	1 (1)

Warnings & Precautions

Palbociclib can cause Neutropenia, Interstitial Lung Disease/Pneumonitis and Embryo-Fetal Toxicity. For more information, please see full US prescribing information at https://labeling.pfizer.com/ShowLabeling.aspx?id=2191.

In the palbociclib + fulvestrant arm, neutropenia, anemia, leukopenia, infections and fatigue were the most common any grade AEs

*Data cut-off: Interim analysis – December 05, 2014; final safety analysis – March 16, 2015.
Clinical Trial Identification: NCT01942135
Final safety analysis: Data cut-off – March 16, 2015 AEs were characterized and graded according to NCI-CTCAE – Grade 1: (<LLN to 1.5 x 10^9/L), Grade 2: (<1.5 to 1.0 x 10^9/L), Grade 3: (<1.0 to 0.5 x 10^9/L), Grade 4: (<0.5 x 10^9/L).
Abbreviations: AE=Adverse Event; LLN=Lower Limit of Normal; NCI-CTCAE: US National Cancer Institute Common Terminology Criteria for Adverse Events.
Reference: Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol.* 2016;17(4):425-439.

MONALEESA-3
Study Design

Multicenter, double-blind, randomized, placebo-controlled, phase 3 study[1-4]

Key Eligibility Criteria

- Age ≥18 years
- Postmenopausal women and men with HR+, HER2- ABC
- Prior (neo)adjuvant ET allowed[a]
- ECOG PS: 0 or 1

2:1 Randomization (N=726)

Ribociclib[1-4]
600 mg/day for 3 wks,
1 wk off over 28-day cycle
+ **Fulvestrant**[b]
(500 mg IM Q4W)
(n=484)

Placebo[1-4]
+ **Fulvestrant**[b]
(500 mg IM Q4W)
(n=242)

Primary Endpoint

- *Investigator-assessed PFS*

Secondary Endpoints

- *OS, ORR, CBR, and safety/tolerability*

Stratification Factors

- *Presence or absence of liver or lung metastases*
- *0-1 line of ET for advanced disease*[a]

[a]First line (ie, therapy-naive for MBC): Relapse >12 months after (neo)adj ET for EBC or de novo MBC with no prior ET. Second line/early relapsers: Early relapse on or ≤12 months after (neo)adj ET or relapse >12 months after (neo)adj ET with PD after first-line ET for MBC or MBC with PD after first-line ET for MBC. [b]Administered on days 1 and 15 of cycle 1.

Clinical Trial Identification: NCT02422615

Abbreviations: ABC=Advanced Breast Cancer; CBR=Clinical Benefit Rate; ECOG PS=Eastern Cooperative Oncology Group Performance Status; ET=Endocrine Therapy; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; IM=Intramuscular; ORR= Overall Response Rate; OS=Overall Survival; PFS=Progression-Free Survival; Q4W=Every 4 Weeks; wk=week

References: 1. Neven P, Fasching PA, Chia S, et al. Updated overall survival from the MONALEESA-3 trial in postmenopausal women with HR+/HER2− advanced breast cancer receiving first-line ribociclib plus fulvestrant. *Breast Cancer Res.* 2023; 25:103. 2. Slamon DJ, Neven P, Chia S, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. *J Clin Oncol.* 2018;36(24):2465-2472. 3. Slamon DJ, Neven P, Chia S, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *NEJM.* 2020;382(6):514-524. 4. Slamon DJ, Neven P, Chia S, et al. Ribociclib plus fulvestrant for postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer in the phase III randomized MONALEESA-3 trial: updated overall survival. *Ann Oncol.* 2021;32(8):1015-1024.

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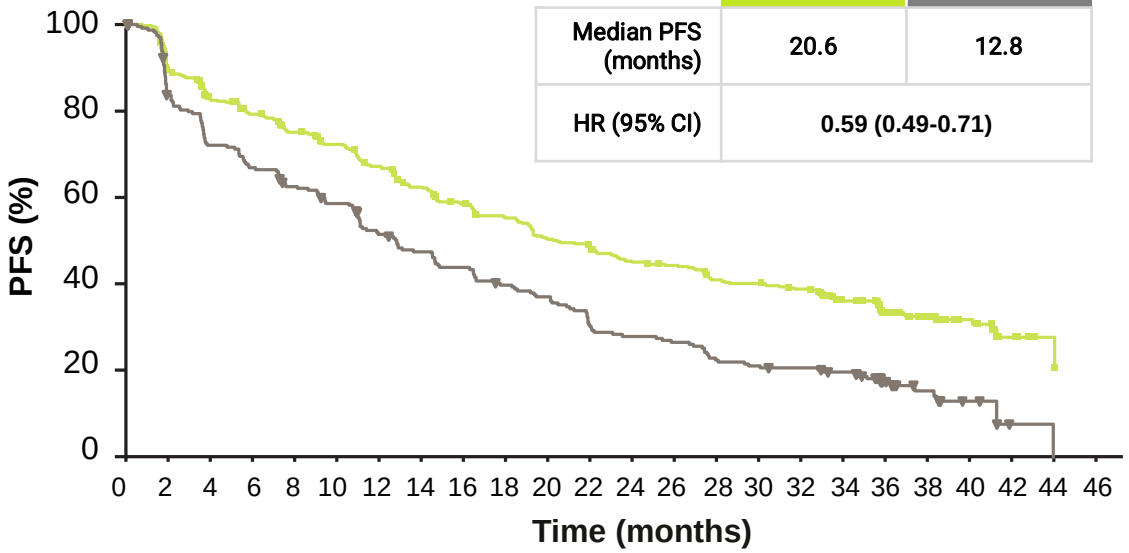
MONALEESA-3
Efficacy Results

Investigator-Assessed PFS[1a]
Updated analysis (descriptive only)

	Ribociclib + Fulvestrant	Placebo + Fulvestrant
Median PFS (months)	20.6	12.8
HR (95% CI)	0.59 (0.49-0.71)	

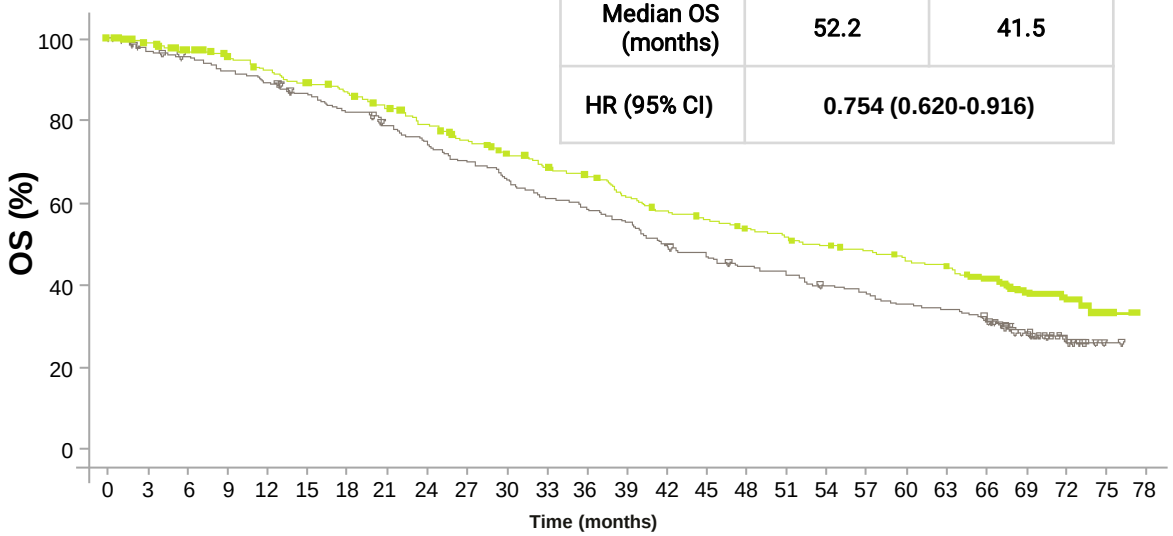


No. at Risk

Ribociclib	484	403	364	346	323	305	282	258	239	225	205	198	181	174	159	156	149	127	92	52	29	11	4	0
Placebo	242	195	168	156	144	134	116	106	98	88	82	68	62	62	59	47	45	41	21	13	6	2	1	0

OS (ITT Population)[2b]
Updated analysis

	Ribociclib + Fulvestrant	Placebo + Fulvestrant
Median OS (months)	52.2	41.5
HR (95% CI)	0.754 (0.620-0.916)	



No. at Risk

Ribociclib	484	461	446	435	415	401	390	369	349	328	310	294	285	262	245	236	224	215	206	199	187	181	163	97	47	8	0
Placebo	242	228	223	215	208	199	188	179	170	158	149	138	133	125	112	105	99	94	87	83	77	74	68	38	14	1	0

In the updated analyses, ribociclib + fulvestrant demonstrated a significantly longer mPFS[a] and mOS than fulvestrant alone in patients with HR+, HER2- ABC

[a]Updated PFS analysis data cut-off: November 3, 2017. Median duration of follow-up: 39.4 months.[1] Primary PFS analysis was reported previously and was statistically significant: mPFS 20.5 months for ribociclib + fulvestrant vs 12.8 months placebo + fulvestrant (HR 0.593 (0.480-0.732) *P*<0.001)[3]

[b]Updated OS analysis data cut-off: January 12, 2022. Median duration of follow-up: 70.8 months.

Clinical Trial Identification: NCT02422615

Abbreviations: ABC=Advanced Breast Cancer; CI=Confidence Interval; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; HR=Hazard Ratio; ITT=Intention to Treat; mOS=Median Overall Survival; mPFS=Median Progression-Free Survival.

References: 1. Slamon DJ, Neven P, Chia S, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *NEJM.* 2020;382(6):514-524. 2. Neven P, Fasching PA, Chia S, et al. Updated overall survival from the MONALEESA-3 trial in postmenopausal women with HR+/HER2− advanced breast cancer receiving first-line ribociclib plus fulvestrant. *Breast Cancer Res.* 2023; 25:103. 3. Slamon DJ, Neven P, Chia S, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. *J Clin Oncol.* 2018;36(24):2465-2472.

MONALEESA-3

*Safety Results**

Adverse events of special interest among patients treated with ribociclib plus fulvestrant or placebo plus fulvestrant as first-line therapy (safety set)

AESI grouping[a]	Ribociclib + Fulvestrant (n=237)			Placebo + Fulvestrant (n=128)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Hematologic AESIs						
Neutropenia	175 (73.8)	123 (51.9)	20 (8.4)	6 (4.7)	2 (1.6)	0
Leukopenia	77 (32.5)	35 (14.8)	2 (0.8)	2 (1.6)	0	0
Anemia	40 (16.9)	6 (2.5)	0	12 (9.4)	2 (1.6)	0
Thrombocytopenia	16 (6.8)	0	0	3 (2.3)	0	0
Other	1 (0.4)	1 (0.4)	0	0	0	0
Nonhematologic AESIs						
Infections	146 (61.6)	21 (8.9)	0	65 (50.8)	6 (4.7)	0
Hepatobiliary toxicity	63 (26.6)	26 (11.0)	6 (2.5)	22 (17.2)	5 (3.9)	0
Renal toxicity	30 (12.7)	2 (0.8)	0	10 (7.8)	0	0
QT interval prolongation	25 (10.5)	12 (5.1)	0	1 (0.8)	1 (0.8)	0
ILD/Pneumonitis	8 (3.4)	2 (0.8)	0	1 (0.8)	0	0
Reproductive toxicity	1 (0.4)	0	0	1 (0.8)	0	0

Warnings & Precautions

Ribociclib can cause Interstitial Lung Disease/Pneumonitis, Severe Cutaneous Adverse Reactions, QT Interval Prolongation, Hepatobiliary Toxicity, Neutropenia, and Embryo-Fetal Toxicity. For more information, please see full US prescribing information at https://www.novartis.us/sites/www.novartis.us/files/kisqali.pdf.

In the ribociclib + fulvestrant arm, neutropenia, leukopenia and anemia were the most common any grade hematologic AEs whereas, infections, hepatobiliary toxicity, renal toxicity and QT interval prolongation were the most common any grade non-hematologic AEs

*Primary safety analysis: Data cut-off – November 3, 2017; Exploratory OS analysis: Data cut-off – January 12, 2022.
[a]Patients with multiple events in a grouping are counted only once in the grouping under the maximum grade.
Clinical Trial Identification: NCT02422615
Abbreviations: AE=Adverse Event; AESI=Adverse events of special interest; ILD, interstitial lung disease.
References: Neven P, Fasching PA, Chia S, et al. Updated overall survival from the MONALEESA-3 trial in postmenopausal women with HR+/HER2− advanced breast cancer receiving first-line ribociclib plus fulvestrant. *Breast Cancer Res.* 2023; 25:103.

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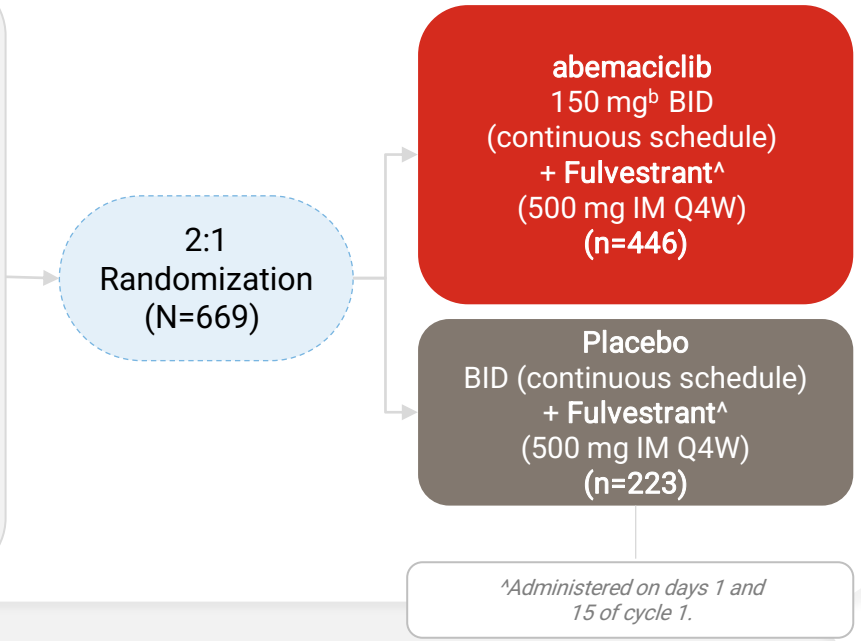
MONARCH 2
Study Design

Multicenter, double-blind, randomized, placebo-controlled, phase 3 study[1,2]

Key Eligibility Criteria

- Women, of any menopausal status with HR+, HER2- ABC
- ET-resistant
  - *Relapsed on neoadjuvant or on/within 1 year of adjuvant ET*
  - *Progressed on first-line ET*
- ≤1 ET and no prior CT for advanced disease
- ECOG PS: 0 or 1



Primary Endpoint

- *Investigator-assessed PFS*

Secondary Endpoints

- *OS, ORR, CBR, DoR, safety, and tolerability*

Stratification Factors

- *Metastatic site (visceral, bone only, or other)*
- *ET resistance (primary or secondary)[3]*

[a]Pre/perimenopausal participants received a gonadotropin-releasing hormone agonist.
[b]Patients received abemaciclib 200 mg BID as per the initial protocol. Dose reduced by protocol amendment after review of data on dose-reduction rates and safety in all new and ongoing patients from 200 mg to 150 mg BID.
Clinical Trial Identification: NCT02107703
Abbreviations: ABC=Advanced Breast Cancer; BID=Twice Daily; CBR=Clinical Benefit Rate; CT=Chemotherapy; DoR=Duration of Response; ECOG PS=Eastern Cooperative Oncology Group Performance Status; ET=Endocrine Therapy; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; IM=Intramuscular; ORR=Objective Response Rate; OS=Overall Survival; PFS=Progression-Free Survival; Q4W=Every 4 Weeks.
References: 1. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+, HER2- advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol.* 2017;35(25):2875-2884. 2. Sledge GW Jr, Toi M, Neven P, et al. 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. *JAMA Oncol.* 2019;6(1):116-124. 3. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol.* 2020;31(12):1623-1649.

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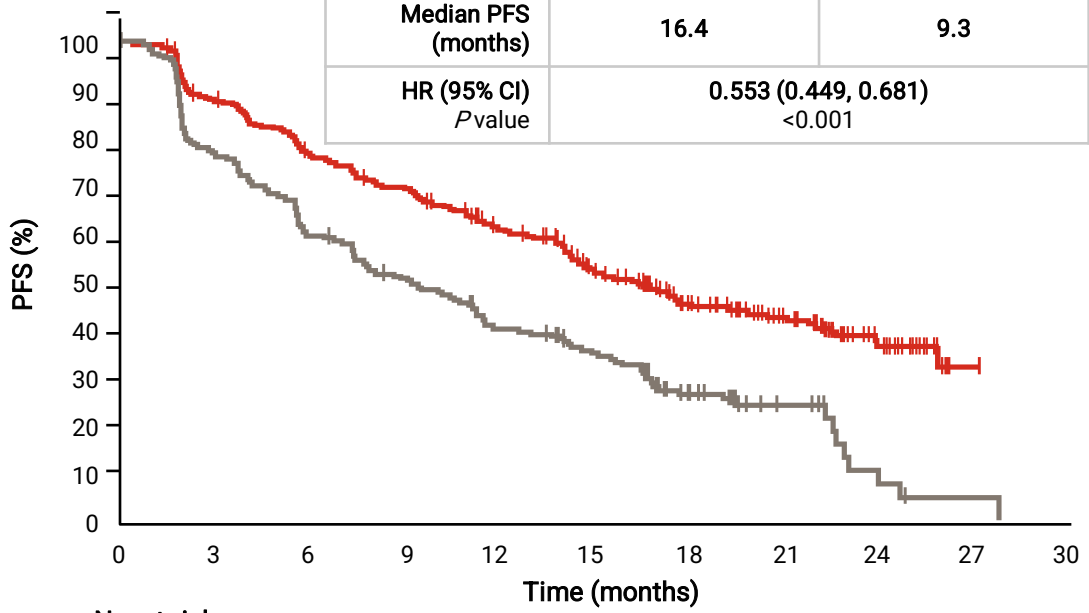
MONARCH 2
Efficacy Results

Primary PFS Analysis[1a]

	Abemaciclib + Fulvestrant	Placebo + Fulvestrant
Median PFS (months)	16.4	9.3
HR (95% CI) *P* value	0.553 (0.449, 0.681) <0.001	

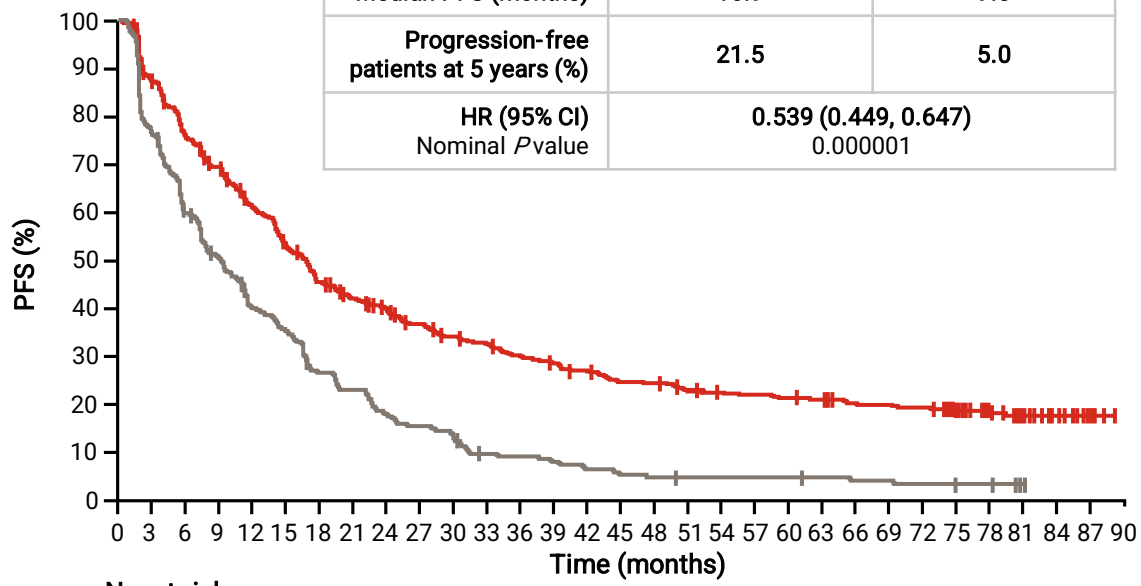


No. at risk

446	367	314	281	234	171	101	65	32	2	0
223	165	123	103	80	61	32	13	4	1	0

Final PFS Analysis[2b]

	Abemaciclib + Fulvestrant	Placebo + Fulvestrant
Median PFS (months)	16.9	9.3
Progression-free patients at 5 years (%)	21.5	5.0
HR (95% CI) Nominal *P* value	0.539 (0.449, 0.647) 0.000001	



No. at risk

446	312	243	177	148	122	105	92	83	73	69	61	59	36	15	0
223	124	81	53	36	26	17	12	9	8	8	6	5	4	0	0

Abemaciclib plus fulvestrant significantly improved PFS in patients with ET-resistant BC: a benefit that was persistent with longer follow-up

[a]Primary endpoint was met at the primary analysis (data cut-off: February 14, 2017). [b]Data cut-off: final PFS – March 18, 2022.
Clinical Trial Identification: NCT02107703.
Abbreviations: BC=breast cancer; CI=Confidence Interval; ET=endocrine therapy; HR=Hazard Ratio; PFS=Progression-Free Survival.
Reference: 1. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+, HER2- advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol.* 2017;35(25):2875-2884. 2. Sledge GW Jr, Toi M, Neven P, et al. Final overall survival analysis of MONARCH 2: A phase 3 trial of abemaciclib plus fulvestrant in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer. Presented at the *45th San Antonio Breast Cancer Symposium 2022*; 6-10 December 2022; San Antonio, TX, USA. Abstract PD13-11.

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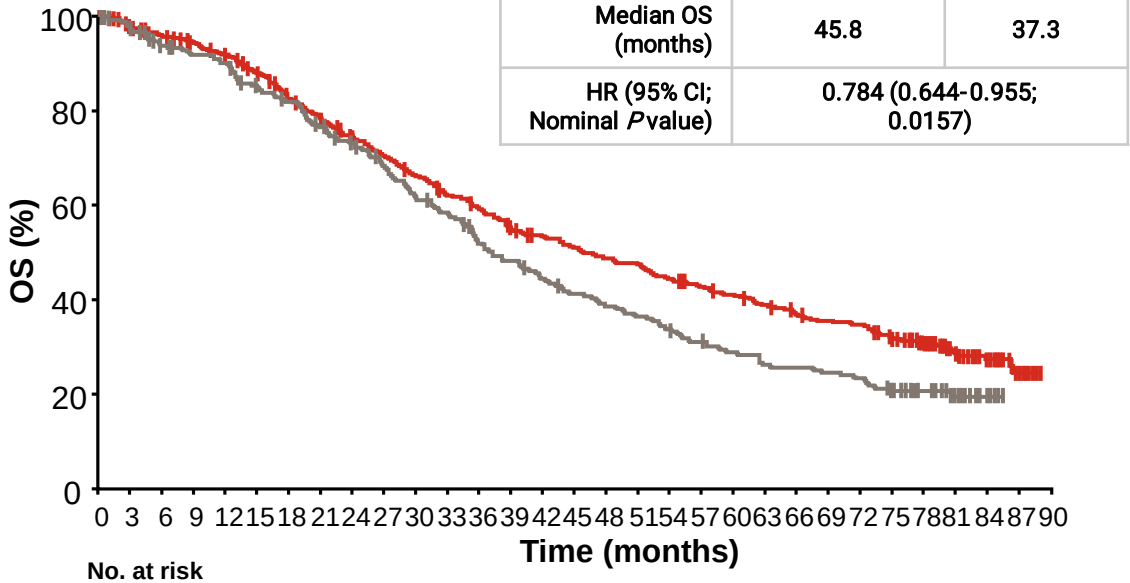
MONARCH 2
*Efficacy Results**

Final OS

	Abemaciclib + Fulvestrant	Placebo + Fulvestrant
Median OS (months)	45.8	37.3
HR (95% CI; Nominal *P* value)	0.784 (0.644-0.955; 0.0157)	



Addition of abemaciclib to fulvestrant reduced the risk of death by 22% in patients with ET-resistant BC at final OS analysis

*Data cut-off: final OS analysis – March 18, 2022.
Clinical Trial Identification: NCT02107703
Abbreviations: BC=Breast Cancer; CI=Confidence Interval; ET=endocrine therapy; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hazard Ratio; OS=Overall Survival.
Reference: Sledge GW Jr, Toi M, Neven P, et al. Final overall survival analysis of MONARCH 2: A phase 3 trial of abemaciclib plus fulvestrant in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer. Presented at the *45th San Antonio Breast Cancer Symposium 2022*; 6-10 December 2022; San Antonio, TX, USA. Abstract PD13-11.

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MONARCH 2
*Safety Results**

TEAEs ≥20% in either arm, n (%)	Abemaciclib + Fulvestrant (n=441)		Placebo + Fulvestrant (n=223)	
	Any Grade	Grade 3+4	Any Grade	Grade 3+4
Any AEs	435 (98.6)	291 (66.0)	203 (91.0)	60 (26.9)
Diarrhea	384 (87.1)	64 (14.5)	62 (7.8)	1 (0.4)
Neutropenia	219 (49.7)	131 (29.7)	9 (4.0)	4 (1.7)
Nausea	217 (49.2)	12 (2.7)	56 (25.1)	5 (2.2)
Fatigue	189 (42.9)	18 (4.1)	64 (28.7)	2 (0.9)
Abdominal pain	164 (37.2)	14 (3.2)	37 (16.6)	2 (0.9)
Anemia	153 (34.7)	40 (9.0)	10 (4.5)	3 (1.3)
Leukopenia	146 (33.1)	49 (11.1)	4 (1.8)	0
Decreased appetite	127 (28.8)	5 (1.1)	30 (13,5)	1 (0.4)
Vomiting	127 (28.8)	4 (0.9)	26 (11.7)	5 (2.2)
Headache	106 (24.0)	3 (0.7)	36 (16.1)	1 (0.4)

Warnings & Precautions

Abemaciclib can cause diarrhea, neutropenia, interstitial lung disease/pneumonitis, hepatoxicity, venous thromboembolism, and embryo-fetal toxicity. For more information, please refer to the full US prescribing information at https://uspl.lilly.com/verzenio/verzenio.html#pi

In the abemaciclib + fulvestrant arm, the most common Any Grade TEAEs were diarrhea, neutropenia, nausea, fatigue, and abdominal pain.

*Data cut-off: Primary safety analysis – February 14, 2017.
Clinical Trial Identification: NCT02107703
AEs were characterized and graded according to NCI-CTCAE – Grade 1: (<LLN to 1.5 x 10^9/L), Grade 2: (<1.5 to 1.0 x 10^9/L), Grade 3: (<1.0 to 0.5 x 10^9/L), Grade 4: (<0.5 x 10^9/L).
Abbreviations: AE=Adverse Event; LLN=Lower Limit of Normal; NCI-CTCAE: US National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE=Treatment-Emergent Adverse Event
Reference: 1. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2– Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapya randomized clinical trial. *J Clin Oncol.* 2017;35:2875-2884. 2. Verzenio [package insert]. Indianapolis, IN: Eli Lilly and Company; 2024. https://uspl.lilly.com/verzenio/verzenio.html#pi

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CDK 4 & 6 Inhibitor Monotherapy

- **MONARCH 1**

Abbreviation:
CDK=Cyclin-Dependent Kinase.

MONARCH 1
Study Design

Multicenter, phase 2, single-arm, open-label study of abemaciclib as a single agent

Key Eligibility Criteria

- HR+, HER2- MBC
- Progressed on or after prior ET
- ≥2 prior CT regimens
  - *1-2 in the metastatic setting*
  - *≥1 taxane either in the adjuvant or metastatic setting*
- ECOG PS: 0 or 1

(N=132)

abemaciclib
200 mg orally
(continuous schedule)
Q12H^

^Administered on days 1 to 28 of a 28-day cycle.

Primary Endpoint

- *ORR*

Secondary Endpoints

- *OS, DoR, PFS, CBR, DCR, and safety/tolerability*

Clinical Trial Identification: NCT02102490
Abbreviations: BID=Twice Daily; CBR=Clinical Benefit Rate; CT=Chemotherapy; DCR=Disease Control Rate; DoR=Duration of Response; ECOG PS=Eastern Cooperative Oncology Group Performance Status; ET=Endocrine Therapy; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; MBC=Metastatic Breast Cancer; ORR=Objective Response Rate; OS=Overall Survival; PFS=Progression-Free Survival; Q12H=Every 12 Hours.
Reference: Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a phase II study of abemaciclib, a CDK 4 & 6 inhibitor, as a single agent, in patients with refractory HR+, HER2- metastatic breast cancer. *Clin Cancer Res*. 2017;23(17):5218-5224. Erratum in: *Clin Cancer Res*. 2018;24(21):5485.

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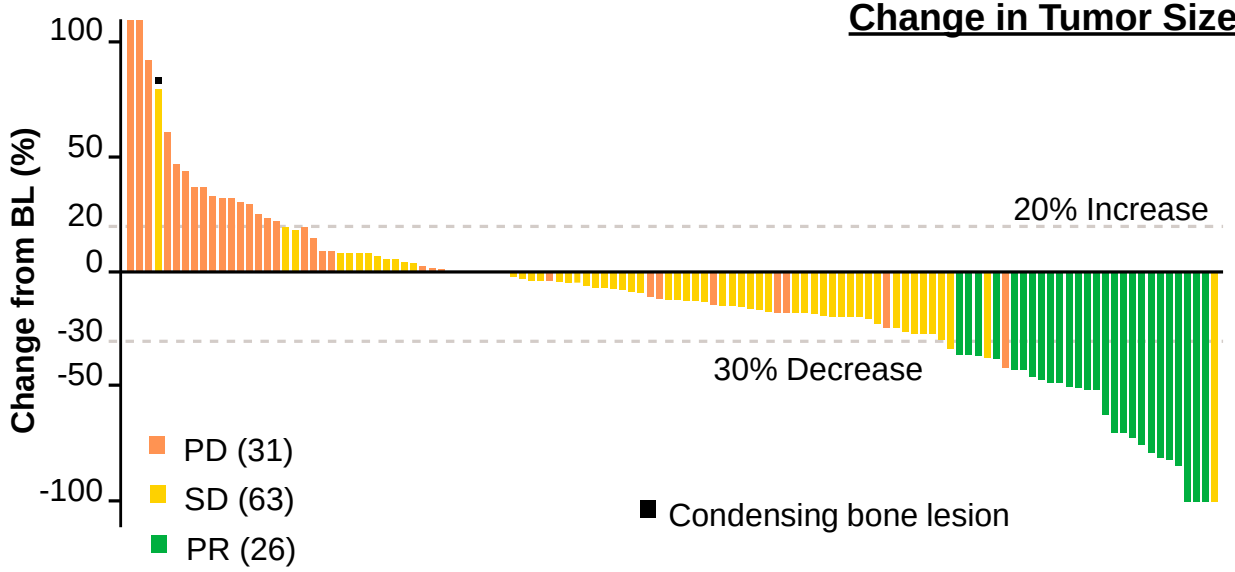
MONARCH 1

*Efficacy Results**

Change in Tumor Size from BL[a]



The colors represent response status per RECIST v1.1 and each bar represents 1 patient.

Abemaciclib 200 mg (N=132) Investigator-Assessed Response,[b] % [95% CI]	
Confirmed ORR • CR • PR	19.7 0 19.7 [13.3-27.5; 15% not excluded]
SD • SD ≥6 mo	47.7 22.7
CBR (ORR + SD ≥6 mo)	42.4

Single-agent treatment with abemaciclib resulted in 20% ORR in heavily pretreated patients with HR+, HER2- MBC

*Data cut-off: April 30, 2016.
[a]For all patients with an available assessment.
[b]Assessments based on independent review were comparable.
Clinical Trial Identification: NCT02102490
Abbreviations: BL=Baseline; CBR=Clinical Benefit Rate; CI=Confidence Interval; CR=Complete Response; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; MBC=Metastatic Breast Cancer; Mo=Month; ORR=Objective Response Rate; PD=Progressive Disease; PR=Partial Response; RECIST=Response Evaluation Criteria in Solid Tumor; SD=Stable Disease.
Reference: Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a phase II study of abemaciclib, a CDK 4 & 6 inhibitor, as a single agent, in patients with refractory HR+, HER2- metastatic breast cancer. *Clin Cancer Res*. 2017;23(17):5218-5224. Erratum in: *Clin Cancer Res*. 2018;24(21):5485.

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MONARCH 1

*Safety Results**

Investigator-Assessed TEAEs ≥20%, %[a]	Abemaciclib (N=132)	
	Any Grade	Grade 3+4
Diarrhea	90.2	19.7
Fatigue	65.2	12.9
Nausea	64.4	4.5
Decreased appetite	45.5	3.0
Abdominal pain	38.6	2.3
Vomiting	34.8	1.5
Headache	20.5	0
Lab abnormalities[b]		
Creatinine increased	98.5	0.8
WBC decreased	90.8	27.7
Neutrophil count decreased	87.7[c]	26.9
Anemia	68.5	0
Platelet count decreased	41.4	2.3
ALT increased	30.0	3.8
ALP increased	26.2	1.5
Hypokalemia	26.2	5.4
Hyponatremia	20.8	3.1

Warnings & Precautions

Abemaciclib can cause diarrhea, neutropenia, interstitial lung disease/pneumonitis, hepatoxicity, venous thromboembolism, and embryo-fetal toxicity. For more information, please refer to the full US prescribing information at https://uspl.lilly.com/verzenio/verzenio.html#pi.

The most common Any Grade TEAEs were diarrhea, creatinine increased, WBC decreased, neutrophil count decreased and anemia

*Data cut-off: April 30, 2016.
Clinical Trial Identification: NCT02102490
[a]Graded as per NCI-CTCAE Version 4.03. [b]N=130 for lab abnormalities listed, except platelet count decreased (N=128). [c]One patient who received cytotoxic chemotherapy within the 30-day follow-up window experienced febrile neutropenia.
Abbreviations: ALP=Alkaline Phosphatase; ALT=Alanine Aminotransferase; NCI-CTCAE=US National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE=Treatment-Emergent Adverse Event; WBC=White Blood Cell.
Reference: Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a phase II study of abemaciclib, a CDK 4 & 6 inhibitor, as a single agent, in patients with refractory HR+, HER2- metastatic breast cancer. *Clin Cancer Res*. 2017;23(17):5218-5224. Erratum in: *Clin Cancer Res*. 2018;24(21):5485.

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Summary (CDK4/6i)

CDK4/6i in combination with endocrine therapy have demonstrated a significantly longer mPFS than endocrine therapy alone across multiple trials in patients with HR+, HER2- ABC or MBC.

Statistically significant OS benefit has been observed in the MONALEESA-2, MONALEESA-3, MONALEESA-7 and MONARCH 2 trials.

Abemaciclib has demonstrated clinical activity as a monotherapy (20% ORR) in heavily pretreated patients with HR+, HER2- MBC

Safety profiles differ between the CDK 4/6i, with neutropenia being the most common AE associated with both palbociclib and ribociclib and diarrhea being the most common AE associated with abemaciclib.

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Abbreviations:
ABC=Advanced Breast Cancer; AE=Adverse Event; CDK=Cyclin-Dependent Kinase; CDKi=Cyclin-Dependent Kinase Inhibitor; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; MBC=Metastatic Breast Cancer; mPFS=Median Progression-Free Survival; ORR=Objective Response Rate; OS=Overall Survival.

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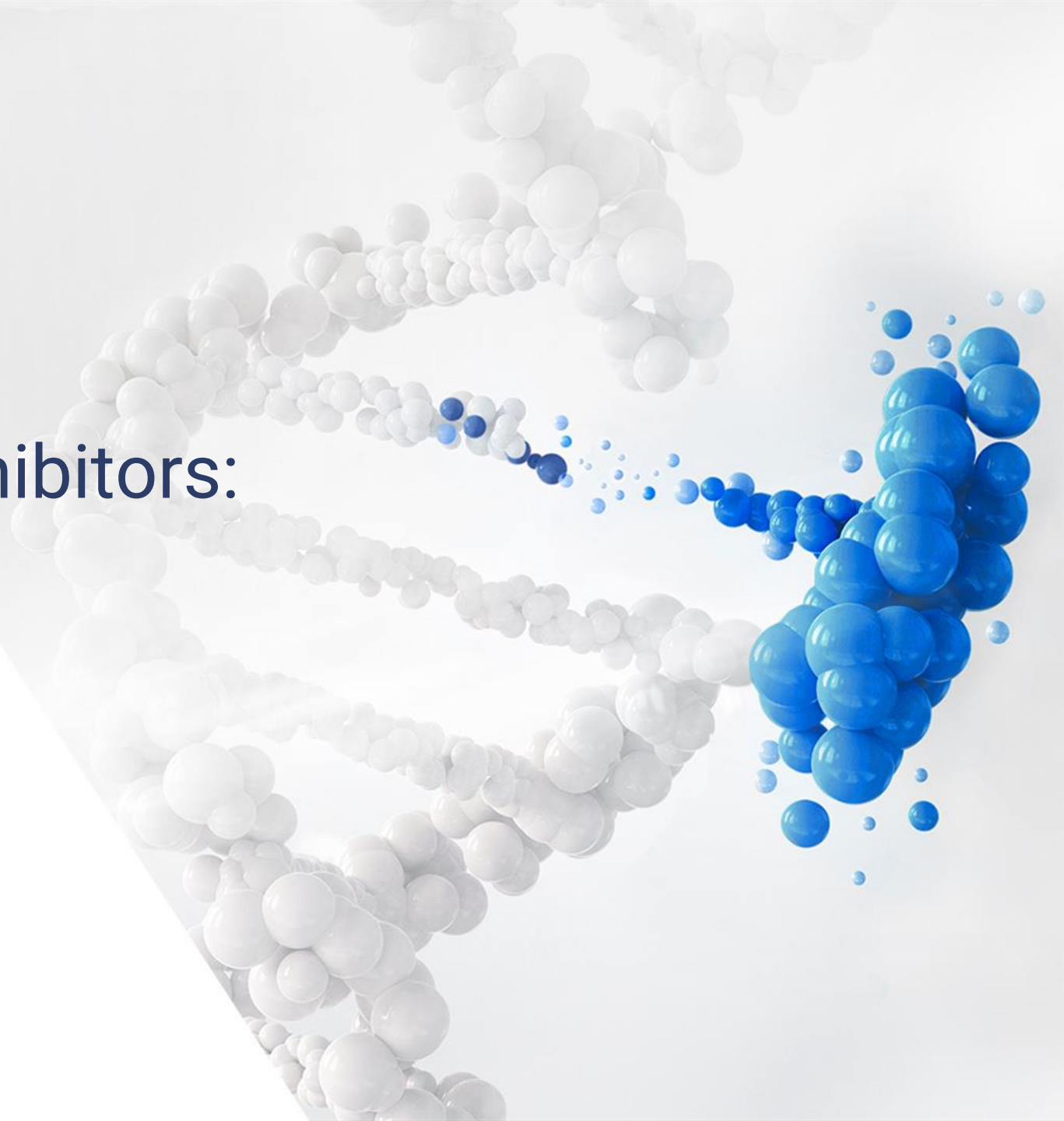
PI3K, AKT, and mTOR Inhibitors: An Overview



Abbreviations:
PI3K=Phosphoinositide-3-Kinase; mTOR=Mammalian Target of Rapamycin.

PI3K, AKT, and mTOR: Role in Cancer

The PI3K/AKT/mTOR signaling pathway activation is central to various cellular processes, including cell proliferation, survival, and angiogenesis (responsible for tumorigenesis)[1,2]

PI3Ks

- *PI3Ks (lipid kinases) are grouped into 3 classes based on their structural characteristics and substrate specificities. Of these 3 classes, the most studied are the class I enzymes, which are further subgrouped into classes IA and IB.[1,2]*
- *Class IA PI3Ks are heterodimers with p110 (catalytic) and p85 (regulatory) subunits. There are 3 genes in mammals, PIK3CA, PIK3CB, and PIK3CD (primarily expressed in leukocytes), encoding the p110 catalytic isoforms: p110α, p110β, and p110δ, respectively.[1,2]*
- *About 25-40% of patients with breast cancer have activating mutations in PIK3CA that can induce p110α-mediated hyperactivation of PI3K.[3]*
- *Alpelisib is an α-specific PI3K inhibitor that selectively inhibits p110α.[4]*

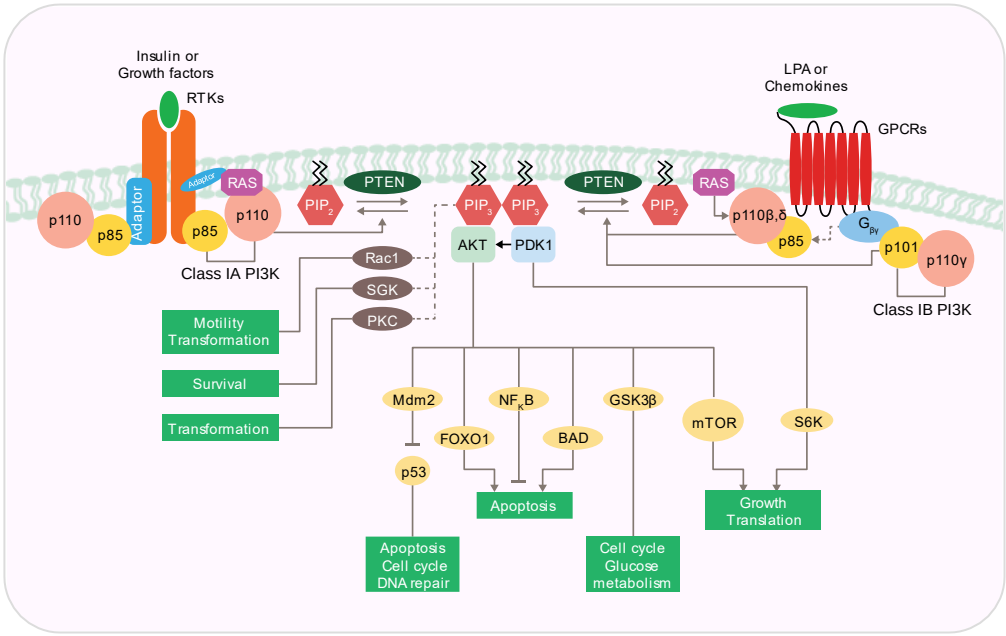
AKT

- *AKT pathway activation occurs in many HR+/HER2− ABC through alterations in PIK3CA, PI3K, mTOR, AKT1 and PTEN, but may also occur in cancers without those genetic alterations.[5,6] AKT signaling is also implicated in the development of resistance to endocrine therapy.[6]*
- *Capivasertib is a potent, selective inhibitor of all three AKT isoforms (AKT1/2/3)[7]*

mTOR

- *Activation of mTOR by AKT (through phosphorylation) plays a critical role in the regulation of cell growth and proliferation.[1,2]*
- *Everolimus is a sirolimus derivative involved in the inhibition of mTOR.[8]*

An Overview of the PI3K, AKT and mTOR Signaling Pathway



Abbreviations: AKT=AKT Serine/Threonine Kinase; BAD=BCL-2-Associated Death Promoter Protein; DNA=Deoxyribonucleic Acid; FOXO1=Forkhead Box O1; G βγ=Guanine Nucleotide Binding Protein (G protein), βγ; NFκB=Nuclear Factor Kappa Light-Chain-Enhancer of Activated B cells; SGK=Serum and Glucocorticoid-Inducible Kinase; GSK3β=Glycogen Synthase Kinase 3 Beta; GPCR=G Protein-Coupled Receptor; MDM2=Murine Double-Minute 2; PDK=Phosphoinositide-dependent Protein Kinase; mTOR=Mammalian Target of Rapamycin; PIP2=Phosphatidylinositol (4,5)-Bisphosphate; PIP3=Phosphatidylinositol (3,4,5)-Trisphosphate; PI3K=Phosphoinositide-3-Kinase; PKC=Protein Kinase C; Rac1=RAS-Related C3 Botulinum Toxin Substrate 1; PTEN=Phosphatase and Tensin Homolog; RAS=Rat Sarcoma; RTK=Receptor Tyrosine Kinase; S6K=Ribosomal Protein S6 Kinase; LPA=Lysophosphatidic Acid.

References: 1. Liu P, Cheng H, Roberts TM, Zhao JJ. Targeting the phosphoinositide 3-kinase pathway in cancer. Nat Rev Drug Discov. 2009;8(8):627-644. 2. Baselga J. Targeting the phosphoinositide-3 (PI3) kinase pathway in breast cancer. Oncologist. 2011;16(suppl 1):12-19. 3. Dirican E, Akkiprik M, Özer A. Mutation distributions and clinical correlations of PIK3CA gene mutations in breast cancer. Tumour Biol. 2016;37(6):7033-7045. 4. André F, Ciruelos E, Rubovszky G, et al; SOLAR-1 Study Group. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. NEJM. 2019;380(20):1929-1940. 5. Millis SZ, Ikeda S, Reddy S, at al. Landscape of Phosphatidylinositol-3-Kinase Pathway Alterations Across 19 784 Diverse Solid Tumors. JAMA Oncol 2016;2:1565-1573. 6. Toss A, Piacentini F, Cortesi L, et al. Genomic alterations at the basis of treatment resistance in metastatic breast cancer: clinical applications. Oncotarget. 2018;9:31606-31619. 7. Miller C, Sommavilla R, Barry ST, et al. Pharmacokinetics of the Akt Serine/Threonine Protein Kinase Inhibitor, Capivasertib, Administered to Healthy Volunteers in the Presence and Absence of the CYP3A4 Inhibitor Itraconazole. *Clin Pharmacol Drug Dev.* 2023 Sep;12(9):856-862. 8. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. NEJM. 2012;366(6):520-529.

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PI3K, AKT, and mTOR Inhibitors: Key Characteristics

Characteristic	Alpelisib[1,2]	Capivasertib[3,4]	Everolimus[5,6]
Target	*α*-specific PI3K (p110*α*)	AKT1/2/3	mTOR
Route of administration[1,2]	Oral	Oral	Oral
Dose, mg	300 QD	400 BID	10 QD
Schedule	Continuous	400 mg BID for 4 days, followed by 3 days off	Continuous
Half-life, h	8–9	8.3	30

Abbreviations: AKT=AKT Serine/Threonine Kinase; BID=Twice Daily; h=Hour; mg=Milligram; mTOR=Mammalian Target of Rapamycin; PI3K=Phosphoinositide 3-kinase; QD=Once Daily.

References: 1. André F, Ciruelos E, Rubovszky G, et al; SOLAR-1 Study Group. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. *NEJM*. 2019;380(20):1929-1940. 2. Piqray [US PI]. East Hanover, NJ, USA: Novartis, 2022. https://www.novartis.us/sites/www.novartis.us/files/piqray.pdf (Accessed March 10, 2023). 3. Turner NC, Oliveira M, Howell SJ, et al. CAPItello-291 Study Group. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med*. 2023;388(22):2058-2070. 4. Truqap [US PI]. Wilmington, DE, USA: AstraZeneca, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/218197s000lbl.pdf (Accessed March 10, 2023). 5. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *NEJM*. 2012;366(6):520-529. 6. Afinitor [US PI]. East Hanover, NJ, USA: Novartis, 2022. https://www.novartis.us/sites/www.novartis.us/files/afinitor.pdf (Accessed March 10, 2023).

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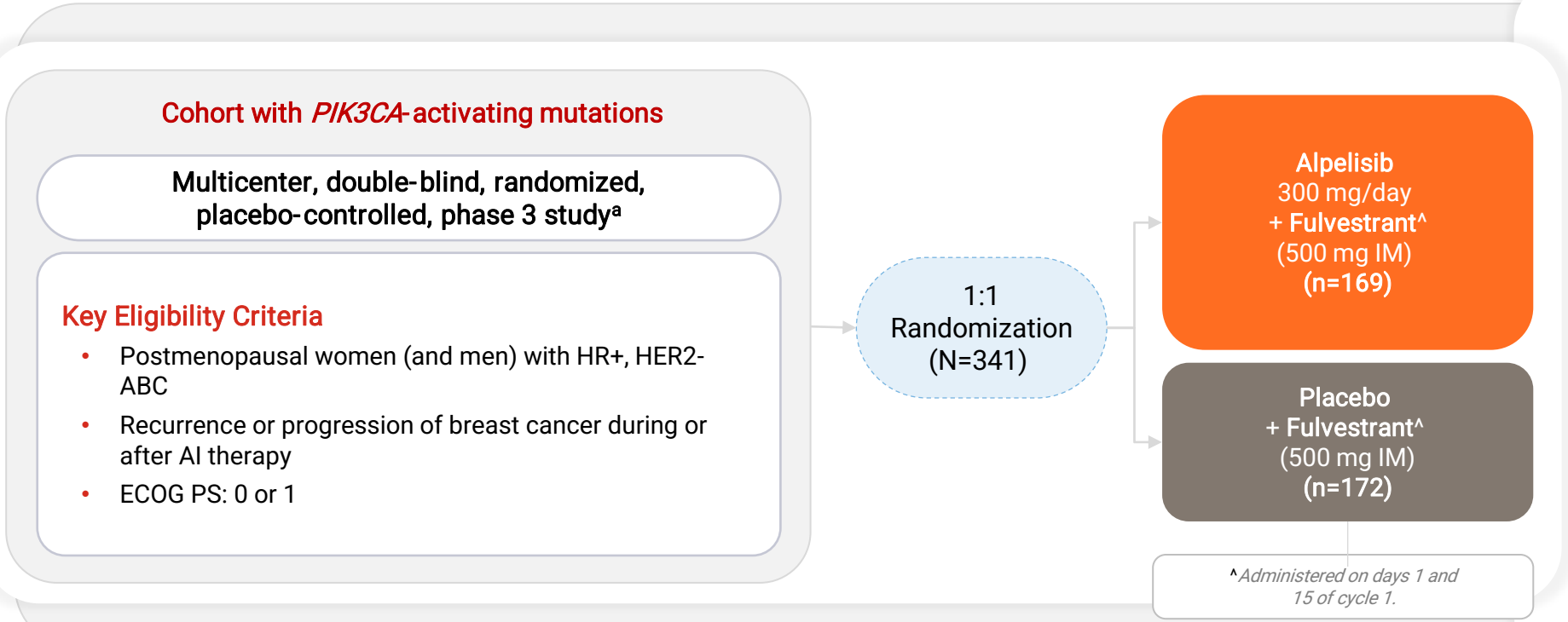
SOLAR-1
Study Design



Primary Endpoint

- *Investigator-assessed PFS*

Secondary Endpoints

- *OS*
- *ORR, CBR, safety*

Stratification Factors

- *Presence or absence of lung or liver metastases*
- *Prior CDK 4 & 6 inhibitor treatment (yes vs. no)*

[a]Patients were enrolled into two cohorts based on tumor-tissue PIK3CA mutation status. The study design for the cohort with PIK3CA-mutated cancer is presented here.

Clinical Trial Identification: NCT02437318

Abbreviations: ABC=Advanced Breast Cancer; AI=Aromatase Inhibitor; CBR=Clinical Benefit Rate; CDK=Cyclin-Dependent Kinase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; IM=Intramuscular; ORR=Objective Response Rate; OS=Overall Survival; PFS=Progression-Free Survival; PIK3CA=Phosphatidylinositol-4,5-Bisphosphate 3-Kinase, Catalytic Subunit Alpha.

Reference: André F, Ciruelos E, Rubovszky G, et al; SOLAR-1 Study Group. Alpelisib for *PIK3CA*-mutated, hormone receptor-positive advanced breast cancer. *NEJM.* 2019;380(20):1929-1940.

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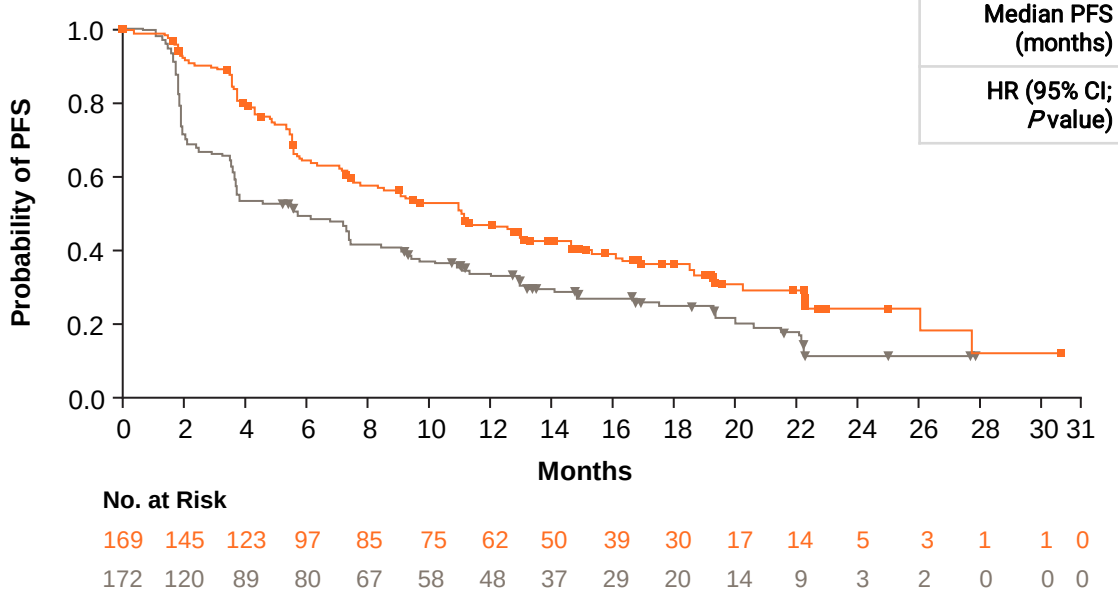
SOLAR-1

*Efficacy Results**

Investigator-Assessed PFS (Cohort With *PIK3CA*-Mutated Cancer)



	Alpelisib + Fulvestrant	Placebo + Fulvestrant
Median PFS (months)	11.0	5.7
HR (95% CI; *P* value)	0.65 (0.50-0.85; <0.001)	

Alpelisib + fulvestrant demonstrated a significantly longer mPFS than fulvestrant alone in patients with HR+, HER2- ABC with a PIK3CA mutation

*Primary endpoint was met at the interim analysis (data cut-off: June 12, 2018).

Clinical Trial Identification: NCT02437318

Abbreviations: ABC=Advanced Breast Cancer; CI=Confidence Interval; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hazard Ratio; HR=Hormone Receptor; mPFS=Median Progression-Free Survival; PFS=Progression-Free Survival; PI3KCA=Phosphatidylinositol-4,5-Bisphosphate 3-Kinase, Catalytic Subunit Alpha.

Reference: André F, Ciruelos E, Rubovszky G, et al; SOLAR-1 Study Group. Alpelisib for *PIK3CA*-mutated, hormone receptor-positive advanced breast cancer. *NEJM.* 2019;380(20):1929-1940.

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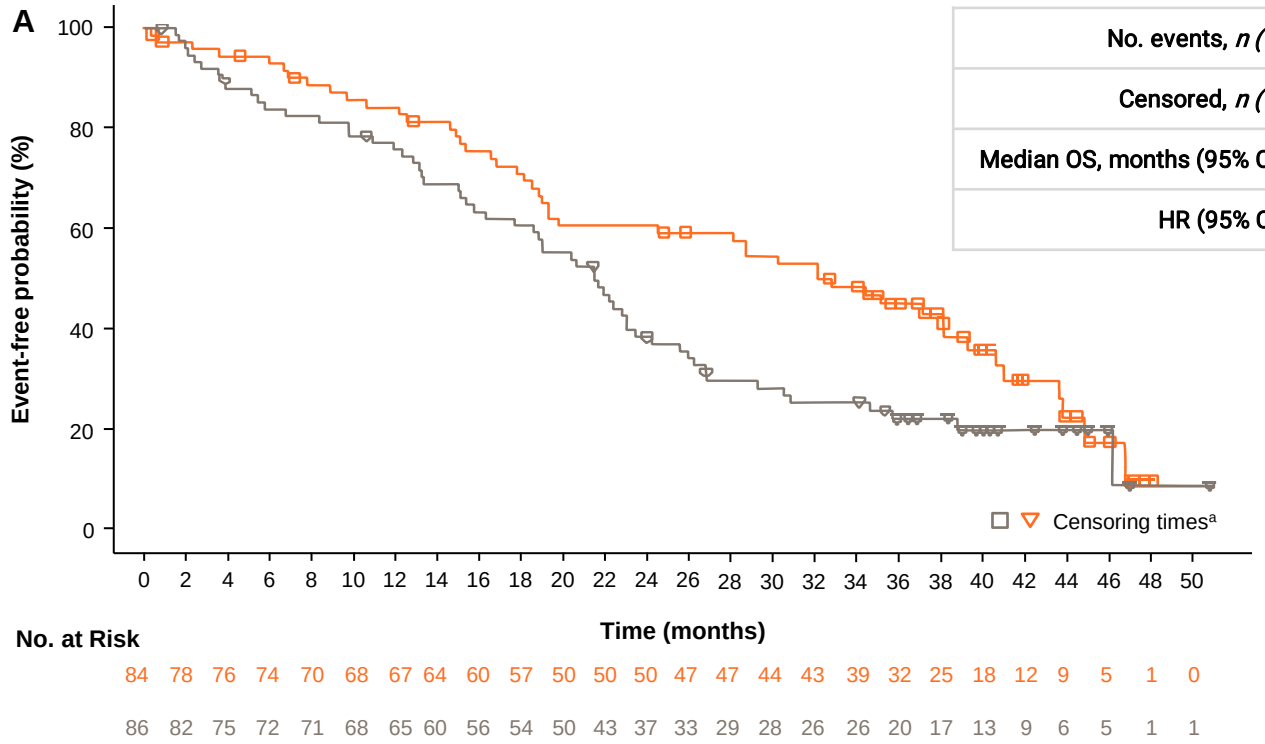
SOLAR-1

*Efficacy Results**

Overall Survival
(Cohort With PIK3CA-Mutated Cancer)



	Alpelisib + FUL (*n* = 84)	Placebo + FUL (*n* = 86)
No. events, *n (%)*	47 (56.0)	58 (67.4)
Censored, *n (%)*	37 (44.0)	28 (32.6)
Median OS, months (95% CI)	37.2 (28.7-43.6)	22.8 (19.0-26.8)
HR (95% CI)	0.68 (0.46-1.00)	

Although the analysis did not cross the prespecified boundary for statistical significance, there was a 7.9-month numeric improvement in median OS when alpelisib was added to fulvestrant treatment of patients with PIK3CA mutated, HR+, HER2- ABC

*Data cut-off: April 23 2020.
Clinical Trial Identification: NCT02437318
Abbreviations: ABC=Advanced Breast Cancer; CI=Confidence Interval; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hazard Ratio; HR=Hormone Receptor; OS=Overall Survival; PI3KCA=Phosphatidylinositol-4,5-Bisphosphate 3-Kinase, Catalytic Subunit Alpha.
Reference: André F, Ciruelos EM, Juric D, et al. Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: final overall survival results from SOLAR-1. *Ann Oncol.* 2021 Feb;32(2):208-217.

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SOLAR-1
*Safety Results**

AEs ≥20% in either arm, n (%)	Alpelisib + Fulvestrant (n=284)		Placebo + Fulvestrant (n=287)	
	Any Grade	Grade 3+4	Any Grade	Grade 3+4
Any AEs	282 (99.3)	216 (76)	264 (92.0)	102 (35.5)
Hyperglycemia[a]	181 (63.7)	104 (36.6)	28 (9.8)	2 (0.7)
Diarrhea[b]	164 (57.7)	19 (6.7)	45 (15.7)	1 (0.3)
Nausea[b]	127 (44.7)	7 (2.5)	64 (22.3)	1 (0.3)
Decreased appetite	101 (35.6)	2 (0.7)	30 (10.5)	1 (0.3)
Rash[c]	101 (35.6)	28 (9.9)	17 (5.9)	1 (0.3)
Vomiting[b]	77 (27.1)	2 (0.7)	28 (9.8)	1 (0.3)
Weight loss	76 (26.8)	11 (3.9)	6 (2.1)	0
Stomatitis	70 (24.6)	7 (2.5)	18 (6.3)	0
Fatigue	69 (24.3)	10 (3.5)	49 (17.1)	3 (1.0)
Asthenia	58 (20.4)	5 (1.8)	37 (12.9)	0

Warnings & Precautions

Alpelisib can cause severe hypersensitivity, severe cutaneous adverse reactions, hyperglycemia, pneumonitis, diarrhea, and embryo-fetal toxicity. For more information, please refer to the full US prescribing information at https://www.novartis.us/sites/www.novartis.us/files/piqray.pdf.

In the alpelisib + fulvestrant arm, the most common Any Grade AEs were hyperglycemia, diarrhea, nausea, decreased appetite and rash

*Data cut-off: Primary analysis – June 12, 2018. Safety data are from the overall SOLAR-1 population, including the PIK3CA mutated and non-mutated cohorts.
Clinical Trial Identification: NCT02437318. **Safety analysis: Data cut-off – June 12, 2018** AEs were characterized and graded according to NCI-CTCAE – Grade 1: (<LLN to 1.5 x 10^9/L), Grade 2: (<1.5 to 1.0 x 10^9/L), Grade 3: (<1.0 to 0.5 x 10^9/L), Grade 4: (<0.5 x 10^9/L). *Safety analysis included all the patients who received at least 1 dose of any study agent; 1 patient who was randomly assigned to the placebo + fulvestrant group did not receive either placebo or fulvestrant. The events that are listed were reported as a single term in at least 15% of the patients for any grade in either group.
[a]AEs of any grade related to hyperglycemia [preferred terms] were reported in 65.8% of the patients in the alpelisib + fulvestrant group and in 10.5% of patients in the placebo + fulvestrant group.
[b]Gastrointestinal toxic effects of any grade (including nausea, vomiting, and diarrhea) were reported in 75.4% of the patients in the alpelisib + fulvestrant group and in 34.8% of patients in the placebo + fulvestrant group.
[c]AEs of any grade related to rash (including rash, rash follicular, rash generalized, and rash maculopapular [preferred terms]) were reported in 53.9% of the patients in the alpelisib + fulvestrant group and in 8.4% of patients in the placebo + fulvestrant group.
Abbreviations: AE=Adverse Event; LLN=Lower Limit of Normal; NCI-CTCAE: US National Cancer Institute Common Terminology Criteria for Adverse Events.
Reference: André F, Ciruelos E, Rubovszky G, et al.; SOLAR-1 Study Group. Alpelisib for *PIK3CA*-mutated, hormone receptor-positive advanced breast cancer. *NEJM.* 2019;380(20):1929-1940.

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CAPItello-291
Study Design

Randomized, double-blind, placebo-controlled, phase 3 study

Key Eligibility Criteria

- Pre-, peri-, and postmenopausal women and men with HR-positive, HER2–negative ABC
- Relapse or disease progression during or after treatment with an AI, with or without previous CDK4/6 inhibitor therapy

1:1 Randomization (N=708)

Capivasertib (400 mg twice daily for 4 days, followed by 3 days off) + **Fulvestrant** (500 mg every 14 days for the first three injections and every 28 days thereafter) **(n=355)**

Placebo + **Fulvestrant** (500 mg every 14 days for the first three injections and every 28 days thereafter) **(n=353)**

Primary Endpoint

- *Investigator-assessed PFS (overall population and in patients with AKT pathway-altered tumors)*

Secondary Endpoints

- *OS, ORR, safety*

Stratification Factors

- *Presence or absence of liver metastases*
- *Previous use of a CDK4/6 inhibitor (yes or no)*
- *Geographic area (assessed in the overall population only)*

Clinical Trial Identification: NCT04305496.
Abbreviations: ABC=Advanced Breast Cancer; AI=Aromatase Inhibitor; CDK= Cyclin-dependent Kinase; HER2=Human Epidermal Growth Factor Receptor 2; HR=hormone receptor; ORR=Objective Response Rate; OS=Overall Survival; PFS=Progression-Free Survival;
References: Turner NC, Oliveira M, Howell SJ, et al. CAPItello-291 Study Group. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med.* 2023;388(22):2058-2070.

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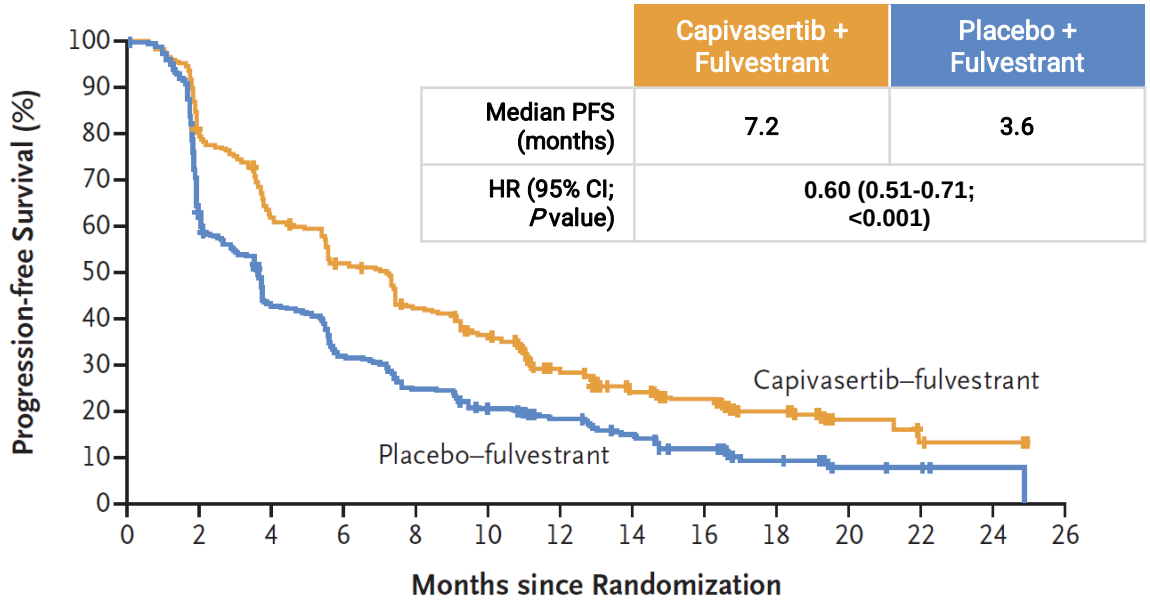
CAPItello-291

*Efficacy Results**

Investigator-Assessed PFS (Overall Population)

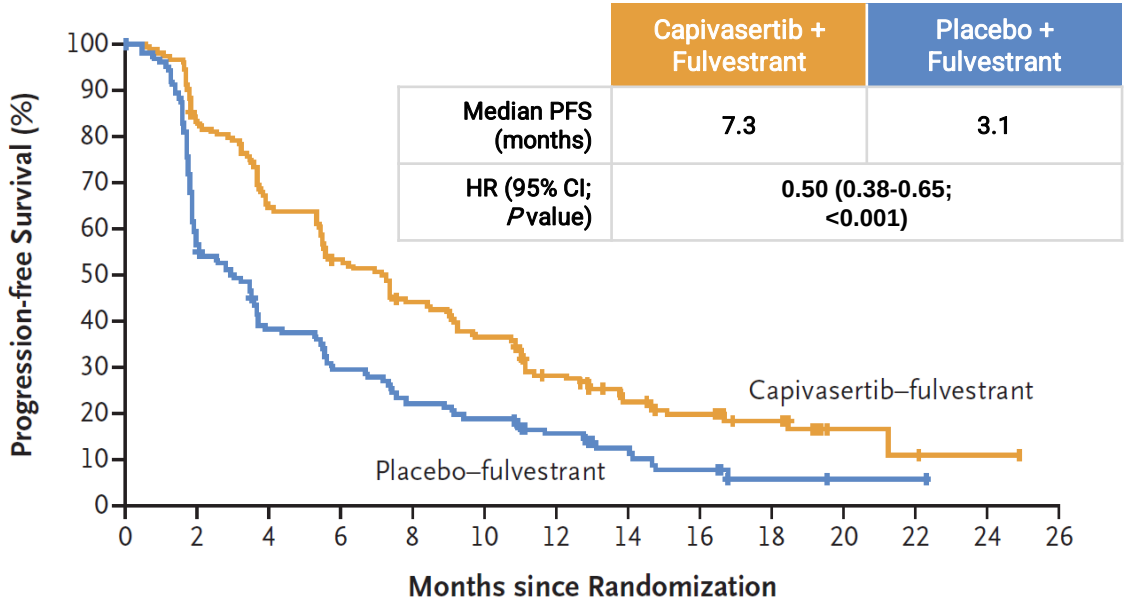


	Capivasertib + Fulvestrant	Placebo + Fulvestrant
Median PFS (months)	7.2	3.6
HR (95% CI; *P* value)	0.60 (0.51-0.71; <0.001)	

No. at Risk

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

Investigator-Assessed PFS (AKT Pathway-Altered Tumors[a])



	Capivasertib + Fulvestrant	Placebo + Fulvestrant
Median PFS (months)	7.3	3.1
HR (95% CI; *P* value)	0.50 (0.38-0.65; <0.001)	

No. at Risk

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

Capivasertib + fulvestrant resulted in significantly longer PFS vs fulvestrant alone in patients with HR+ HER2- ABC with or without AKT pathway-altered tumors whose disease had progressed during or after previous AI therapy with or without a CDK4/6 inhibitor

*Data cut-off: August 15, 2022.
[a]Patients with a *PIK3CA*, *AKT1*, or *PTEN* alteration in tumor.
Clinical Trial Identification: NCT04305496.
Abbreviations: ABC=advanced breast cancer; AI=aromatase inhibitor; CI=Confidence Interval; HR=Hazard Ratio; HER-=Human Epidermal Growth Factor Receptor 2–negative; HR+=Hormone Receptor–Positive; PFS=Progression-Free Survival
Reference: Turner NC, Oliveira M, Howell SJ, et al. CAPItello-291 Study Group. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med.* 2023 Jun 1;388(22):2058-2070.

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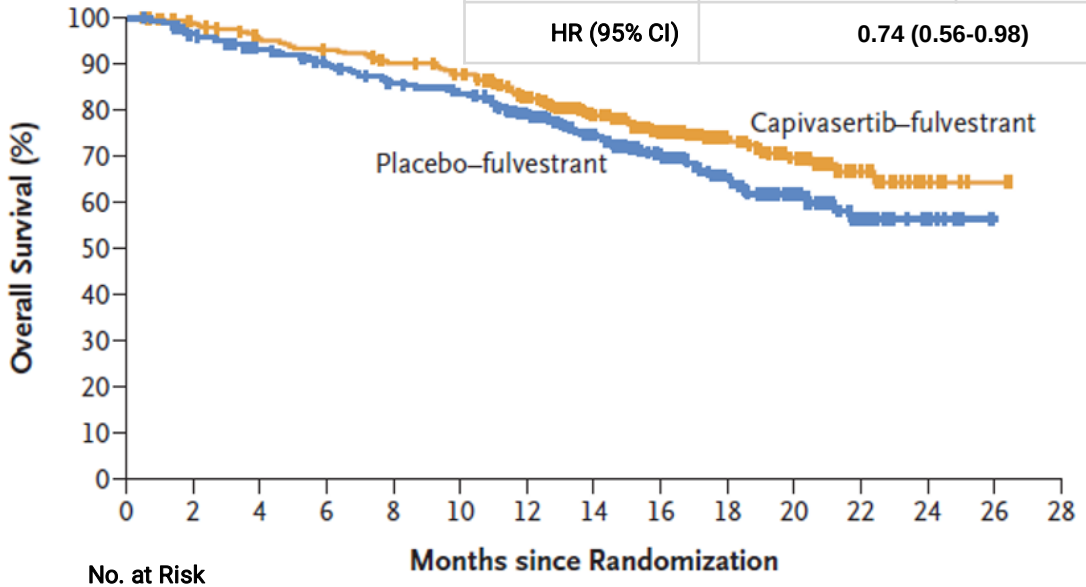
CAPItello-291

*Efficacy Results**

Overall Survival (Overall Population)

	Capivasertib + Fulvestrant	Placebo + Fulvestrant
18-month OS, % (95% CI)	73.9% (68.3 to 78.7)	65.0% (58.7 to 70.6)
HR (95% CI)	0.74 (0.56-0.98)	

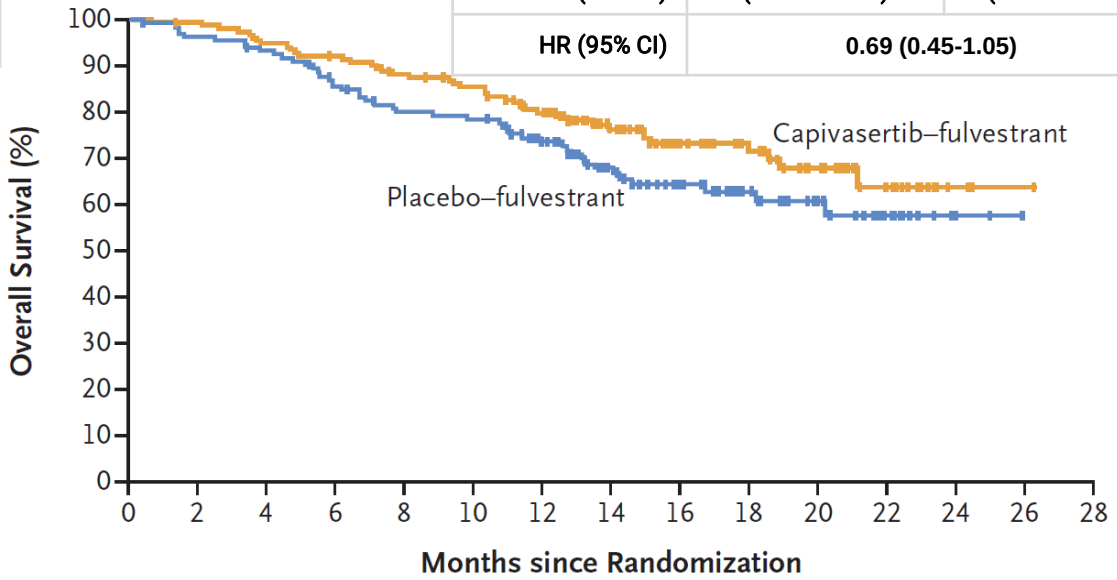


No. at Risk

355	343	327	318	306	295	258	198	144	95	63	33	9	2	0
353	334	316	301	283	274	237	181	134	90	59	30	11	0	0

Overall Survival (AKT Pathway-Altered Tumors[a])

	Capivasertib + Fulvestrant	Placebo + Fulvestrant
18-month OS, % (95% CI)	73.2% (64.8 to 80.0)	62.9% (53.1 to 71.2)
HR (95% CI)	0.69 (0.45-1.05)	



No. at Risk

155	153	144	139	131	125	111	83	60	45	30	14	3	1	0
134	127	122	112	101	99	87	62	46	31	22	13	3	0	0

A sufficient number of deaths for a formal analysis of overall survival had not occurred by the data-cutoff date

*Data cut-off: August 15, 2022.
[a]Patients with a *PIK3CA*, *AKT1*, or *PTEN* alteration in tumor.
Clinical Trial Identification: NCT04305496.
Abbreviations: CI=Confidence Interval; HR=Hazard Ratio; OS=overall survival
Reference: Turner NC, Oliveira M, Howell SJ, et al. CAPItello-291 Study Group. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med.* 2023 Jun 1;388(22):2058-2070.

CAPItello-291

Safety Results (Overall Population)[*,a]

AEs ≥10% in either arm, n (%)	Capivasertib + Fulvestrant (n=355)		Placebo + Fulvestrant (n=350)	
	Any Grade	Grade 3+4	Any Grade	Grade 3+4
Any AEs	343 (96.6)	148 (41.7)	288 (82.3)	54 (15.4)
Diarrhea	257 (72.4)	33 (9.3)	70 (20.0)	1 (0.3)
Rash[b]	135 (38.0)	43 (12.1)	25 (7.1)	1 (0.3)
Nausea	123 (34.6)	3 (0.8)	54 (15.4)	2 (0.6)
Fatigue	74 (20.8)	2 (0.6)	45 (12.9)	2 (0.6)
Vomiting	73 (20.6)	6 (1.7)	17 (4.9)	2 (0.6)
Headache	60 (16.9)	1 (0.3)	43 (12.3)	2 (0.6)
Decreased appetite	59 (16.6)	1 (0.3)	22 (6.3)	2 (0.6)
Hyperglycemia	58 (16.3)	8 (2.3)	13 (3.7)	1 (0.3)
Stomatitis	52 (14.6)	7 (2.0)	17 (4.9)	0 (0.0)
Asthenia	47 (13.2)	4 (1.1)	36 (10.3)	2 (0.6)
Pruritis	44 (12.4)	2 (0.6)	23 (6.6)	0 (0.0)
Anemia	37 (10.4)	7 (2.0)	17 (4.9)	4 (1.1)
Urinary tract infection	36 (10.1)	5 (1.4)	23 (6.6)	0 (0.0)

Warnings & Precautions

Capivasertib can cause hyperglycemia, diarrhea, cutaneous adverse reactions, and embryo-fetal toxicity. For more information, please refer to the full US prescribing information at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/218197s000lbl.pdf

Among patients receiving capivasertib, diarrhea, rash and nausea were the most common adverse events of any grade, occurring in 72.4%, 38.0%, and 34.6% of patients, respectively

*Data cut-off: August 15, 2022.

[a]The safety population included all the patients who received at least one dose of capivasertib, fulvestrant, or placebo. The listed events were reported as a single term (or for rash, as a group term) in at least 10% of the patients for any grade in the capivasertib–fulvestrant group. Adverse events are reported regardless of the relationship to capivasertib, fulvestrant, or placebo.

[b]The group term of rash includes the preferred terms of rash, rash macular, maculopapular rash, rash papular, and rash pruritic.

Clinical Trial Identification: NCT04305496.

Reference: Turner NC, Oliveira M, Howell SJ, et al. CAPItello-291 Study Group. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med.* 2023 Jun 1;388(22):2058-2070.

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BOLERO-2
Study Design

Multicenter, double-blind, randomized, placebo-controlled, phase 3 study[1,2]

Key Eligibility Criteria

- Postmenopausal women with ER+/HER2- ABC whose disease was refractory to previous NSAI
- Other prior ET and a single prior CT for advanced disease were allowed.
- ECOG PS: 0-2

2:1 Randomization (N=724)

Everolimus 10 mg/day + **Exemestane** (25 mg/day) **(n=485)**

Placebo + **Exemestane** (25 mg/day) **(n=239)**

Primary Endpoint

- *Investigator-assessed PFS*

Secondary Endpoints

- *OS, ORR, CBR, time to deterioration of ECOG PS, safety, and QoL*

Stratification Factors

- *Sensitivity to prior ET (yes vs. no)*
- *Presence of visceral metastasis (yes vs. no)*

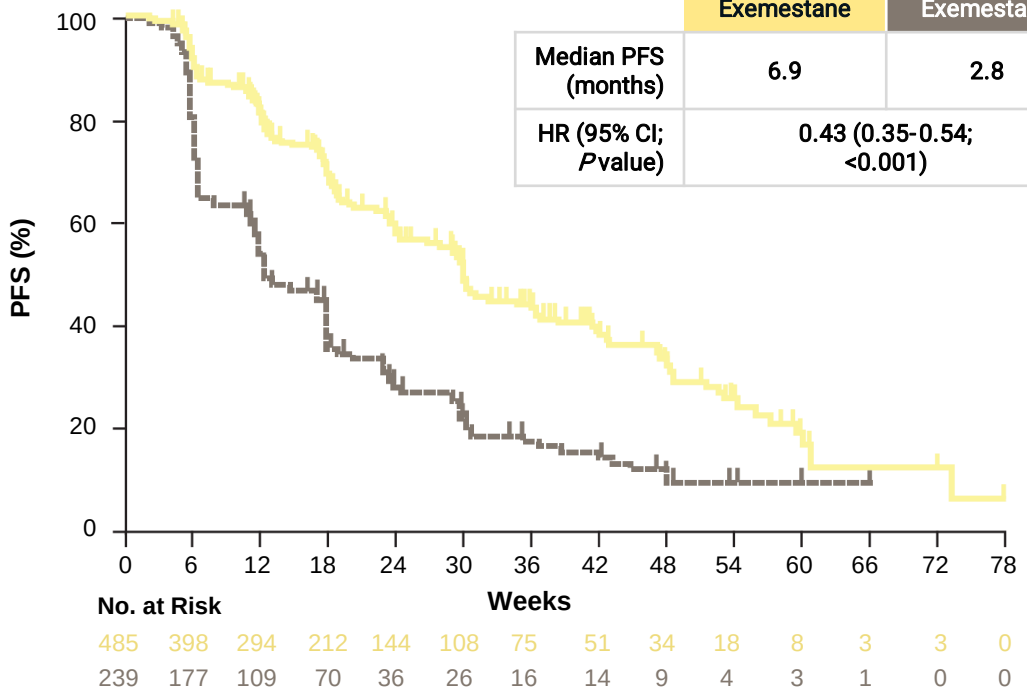
Clinical Trial Identification: NCT00863655

Abbreviations: ABC=Advanced Breast Cancer; CBR=Clinical Benefit Rate; CT=Chemotherapy; ECOG PS=Eastern Cooperative Oncology Group Performance Status; ER=Estrogen Receptor; ET=Endocrine Therapy; HER2=Human Epidermal Growth Factor Receptor 2; NSAI=Non-Steroidal Aromatase Inhibitor; ORR=Objective Response Rate; OS=Overall Survival; PFS=Progression-Free Survival; QoL=Quality of Life.

References: 1. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *NEJM.* 2012;366(6):520-529. 2. Piccart M, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2. *Ann Oncol.* 2014;25(12):2357-2362.

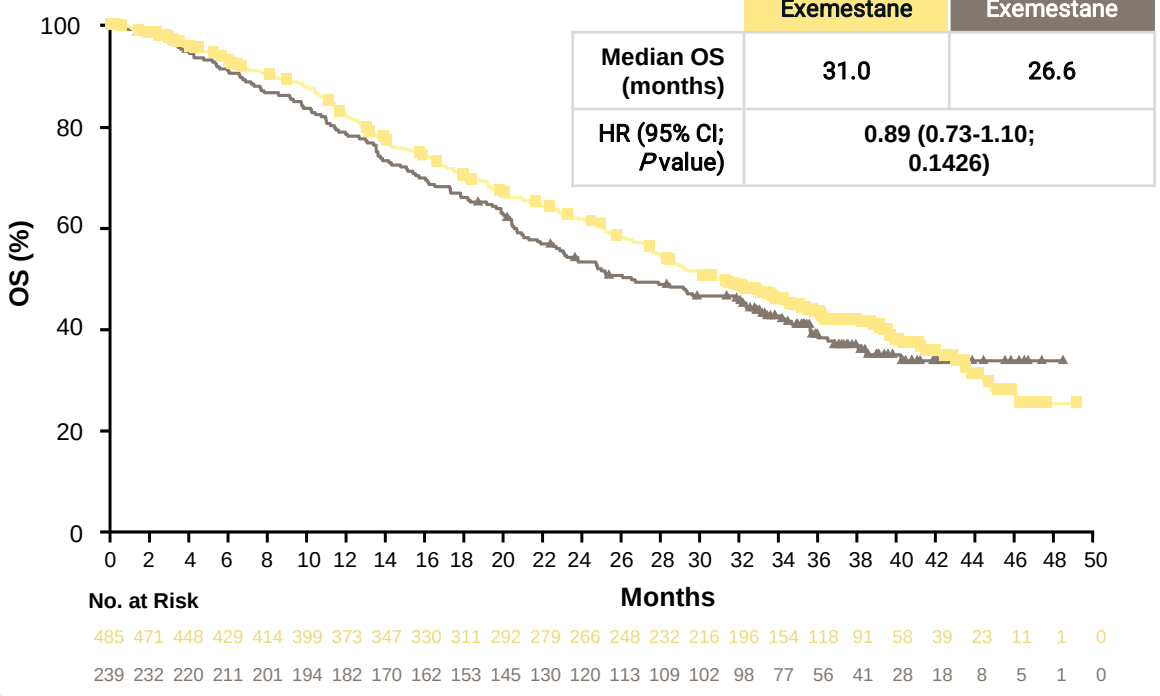
BOLERO-2
*Efficacy Results**

PFS Analysis[1a]



	Everolimus + Exemestane	Placebo + Exemestane
Median PFS (months)	6.9	2.8
HR (95% CI; *P* value)	0.43 (0.35-0.54; <0.001)	

OS Analysis[2]



	Everolimus + Exemestane	Placebo + Exemestane
Median OS (months)	31.0	26.6
HR (95% CI; *P* value)	0.89 (0.73-1.10; 0.1426)	

Everolimus + exemestane demonstrated a significantly longer mPFS than exemestane alone in patients with ER+/HER2- ABC. There was no statistically significant improvement in mOS

*Data cut-off: Interim analysis – February 11, 2011; OS analysis – October 3, 2013.
[a]Primary endpoint was met at the interim analysis (data cut-off: February 11, 2011).
Clinical Trial Identification: NCT00863655
Abbreviations: CI=Confidence Interval; HR=Hazard Ratio; mOS= Median Overall Survival; mPFS=Median Progression-Free Survival; OS=Overall Survival; PFS=Progression-Free Survival.
References: 1. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *NEJM.* 2012;366(6):520-529. 2. Piccart M, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2†. *Ann Oncol.* 2014;25(12):2357-2362.

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BOLERO-2

Safety Results (AEs with ≥20% incidence in the Everolimus-Exemestane Group)*

Adverse Event, %	Everolimus and Exemestane (n=482)			Placebo and Exemestane (n=238)		
	Any Event	Grade 3 Event	Grade 4 Event	Any Event	Grade 3 Event	Grade 4 Event
Stomatitis	56	8	0	11	1	0
Rash	36	1	0	6	0	0
Fatigue	33	3	<1	26	1	0
Diarrhea	30	2	<1	16	1	0
Decreased appetite	29	1	0	10	0	0
Nausea	27	<1	<1	27	1	0
Cough	22	1	0	11	0	0
Dysgeusia	21	<1	0	5	0	0

Warnings & Precautions

Everolimus can cause non-infectious pneumonitis, infections, severe hypersensitivity reactions, angioedema with concomitant use of angiotensin-converting enzyme inhibitors, stomatitis, renal failure, risk of impaired wound healing, increased risk in geriatric patients, metabolic disorders, myelosuppression, risk of infection or reduced immune response with vaccination, radiation sensitization and radiation recall, and embryo-fetal toxicity. For more information, please refer to the full US prescribing information at https://www.novartis.us/sites/www.novartis.us/files/afinitor.pdf.

In the everolimus + exemestane arm, the most common Any Grade AEs were stomatitis, rash, fatigue, diarrhea, decreased appetite, nausea, cough and dysgeusia

*Data cut-off: Safety analysis – February 11, 2011.
Clinical Trial Identification: NCT00863655
Safety analysis: Data cut-off – February 11, 2011
AEs were characterized and graded according to NCI-CTCAE – Grade 1: (<LLN to 1.5 x 10^9/L), Grade 2: (<1.5 to 1.0 x 10^9/L), Grade 3: (<1.0 to 0.5 x 10^9/L), Grade 4: (<0.5 x 10^9/L).
Abbreviations: AE=Adverse Event; LLN=Lower Limit of Normal; NCI-CTCAE: US National Cancer Institute Common Terminology Criteria for Adverse Events.
Reference: Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *NEJM.* 2012;366(6):520-529.

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Summary (PI3Ki/AKTi/mTORi)

01 The PI3K inhibitor, alpelisib, in combination with fulvestrant, demonstrated a significantly longer mPFS than fulvestrant alone in patients with ER+/HER2- ABC and a *PIK3CA* mutation.

02 The AKT inhibitor, capivasertib, in combination with fulvestrant demonstrated a significantly longer mPFS than fulvestrant alone in patients with HR+, HER2- ABC.

03 The mTOR inhibitor, everolimus, in combination with exemestane, demonstrated a significantly longer mPFS than exemestane alone in patients with ER+/HER2- ABC.

04 The most common side effects of alpelisib, capivasertib, and everolimus were hyperglycemia, diarrhea, and stomatitis, respectively.

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Abbreviations:
ABC=Advanced Breast Cancer; ER=Estrogen Receptor; HER2=Human Epidermal Growth Factor Receptor 2; HR=hormone receptor; mPFS=Median Progression-Free Survival; mTOR=Mammalian Target of Rapamycin; mTORi=Mammalian Target of Rapamycin Inhibitor; PI3K=Phosphoinositide-3-Kinase; PI3Ki=Phosphoinositide-3-Kinase Inhibitor; PI3KCA=Phosphatidylinositol-4,5-Bisphosphate 3-Kinase, Catalytic Subunit Alpha.

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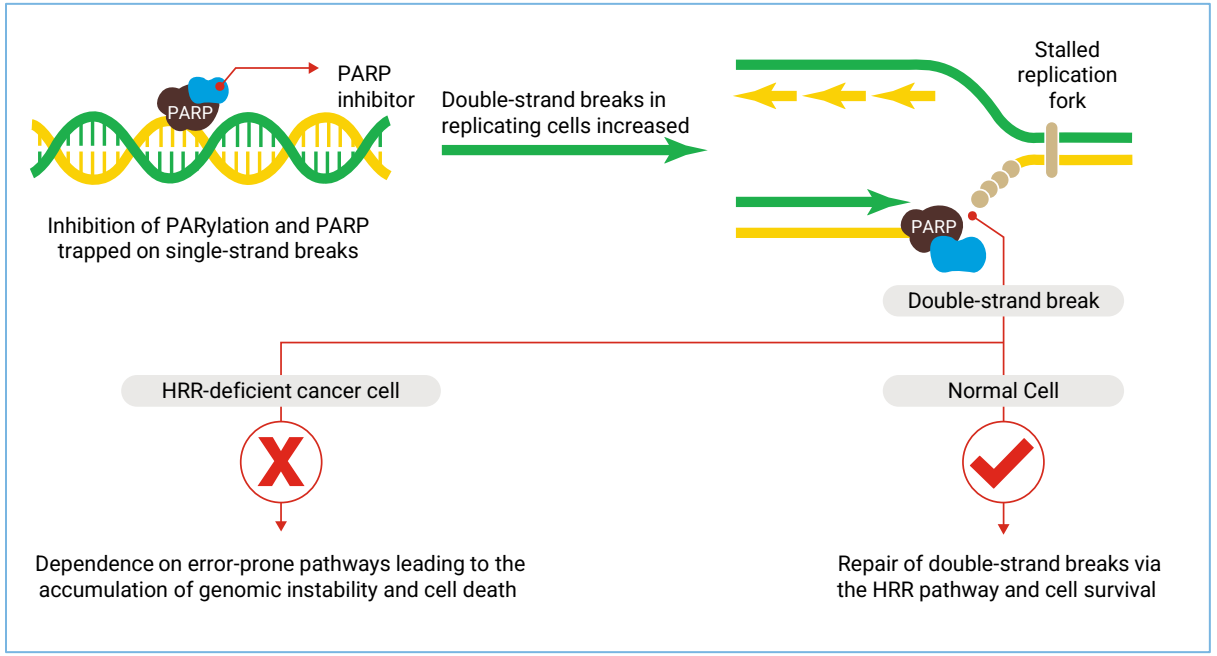
PARP Inhibitors: An Overview

Abbreviation:
PARP=Poly (ADP-Ribose) Polymerase.

DNA Damage Repair Pathway

- Healthy cells protect themselves against DNA damage through 5 major DNA damage response pathways.[1]
- This includes base excision repair that deals with single-strand breaks and homologous recombination repair (HRR) which deals with double-strand breaks.[1]
- PARP enzymes are important for the base excision repair pathway (single-strand breaks). Double-strand breaks are formed when single-strand breaks are not repaired.[1]
- BRCA1/2 proteins play a vital role in the HRR pathway. Inhibition of PARP in BRCA-mutated cells leads to cell death due to synthetic lethality.[1]
- Olaparib and talazoparib monotherapies have been shown to improve PFS in patients with deleterious or suspected deleterious germline BRCA-mutated, HER2- breast cancer.[2,3]



Cortesi L, et al. *Target Oncol.* 2021;16 (3):255-282.

Abbreviations: BRCA1/2=Breast Cancer Gene 1/2; HER2=Human Epidermal Growth Factor Receptor 2; PAR=Poly-(ADP-Ribose); PARP=Poly-(ADP-Ribose) Polymerase; PFS=Progression-Free Survival.

References: 1. Cortesi L, Rugo HS, Jackisch C. An overview of PARP inhibitors for the treatment of breast cancer. *Target Oncol.* 2021;16(3):255-282. 2. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *NEJM.* 2017;377(6):523-533. Erratum in: *NEJM.* 2017;377(17):1700. 3. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *NEJM.* 2018;379(8):753-763.

PARP Inhibitors: Key Characteristics

Characteristic	Olaparib	Talazoparib
Target[1,2]	PARP1, PARP2, PARP3	PARP1, PARP2
Route of administration[1,2]	Oral	Oral
Dose,[1,2] mg	300 BID	1 QD
Schedule[1,2]	Continuous	Continuous
Half-life,[1,2] h	14.9 ± 8.2	90 ± 58

Abbreviations: BID=Twice Daily; h=Hour; mg=Milligram; PARP=Poly-(ADP-Ribose) Polymerase, QD=Once Daily.

References: 1. Lynparza [US PI]. Wilmington, DE, USA: AstraZeneca, 2023. (Accessed Jan 12, 2024). 2. Talzenna [US PI]. New York, NY, USA: Pfizer, 2023. https://labeling.pfizer.com/ShowLabeling.aspx?id=11046 (Accessed Jan 12, 2024).

OlympiAD
Study Design

Multicenter, open-label, randomized, controlled, phase 3 study of olaparib[1,2]

Key Eligibility Criteria

- Patients ≥18 years of age with HER2- MBC
- Deleterious or suspected deleterious germline *BRCA1/2* mutation
- Previous neoadjuvant or adjuvant treatment with an anthracycline and a taxane[a]
- Prior ≥1 hormone therapies for HR+ BC
- ≤2 prior cytotoxic regimens for ABC
- ECOG PS: 0-1

2:1 Randomization (N=302)

- Olaparib 300 mg BID (n=205)
- Standard Chemotherapy[b] [capecitabine, eribulin mesylate, vinorelbine] (n=97)

Primary Endpoint

- *BICR-assessed PFS*

Secondary Endpoints

- *Safety outcomes, OS, ORR, PFS2 and HRQoL*

Stratification Factors

- *Previous use of CT for metastatic disease (yes vs. no)*
- *HR status (triple negative vs. HR+)*
- *Previous use of platinum-based therapy (yes vs. no)*

Clinical Trial Identification: NCT02000622

[a]Disease-free interval of at least 12 months after the last dose. [b]Standard therapy with one of the following 3 prespecified chemotherapy regimens:

1. Capecitabine: Administered orally at a dose of 2500 mg/m^2 of body-surface area daily (divided into 2 doses) for 14 days, repeated every 21 days
2. Eribulin mesylate: Administered IV at a dose of 1.4 mg/m^2 on days 1 and 8, repeated every 21 days
3. Vinorelbine: Administered IV at a dose of 30 mg/m^2 on days 1 and 8, repeated every 21 days

Abbreviations: ABC=Advanced Breast Cancer; BICR=Blinded Independent Central Review; BID=Twice Daily; BRCA1/2=Breast Cancer Susceptibility Genes 1 or 2; BC=Breast Cancer; CT=Chemotherapy; ECOG PS=Eastern Cooperative Oncology Group Performance Status; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; HRQoL=Health-Related Quality of Life; MBC=Metastatic Breast Cancer; ORR=Objective Response Rate; OS=Overall Survival; PFS=Progression-Free Survival; PFS2=Progression-Free Survival on Second/Subsequent Line of Therapy; TNBC=Triple-Negative Breast Cancer.

References: 1. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *NEJM.* 2017;377(6):523-533. Erratum in: *NEJM.* 2017;377(17):1700. 2. Robson ME, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability results: olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Ann Oncol.* 2019;30(4):558-566.

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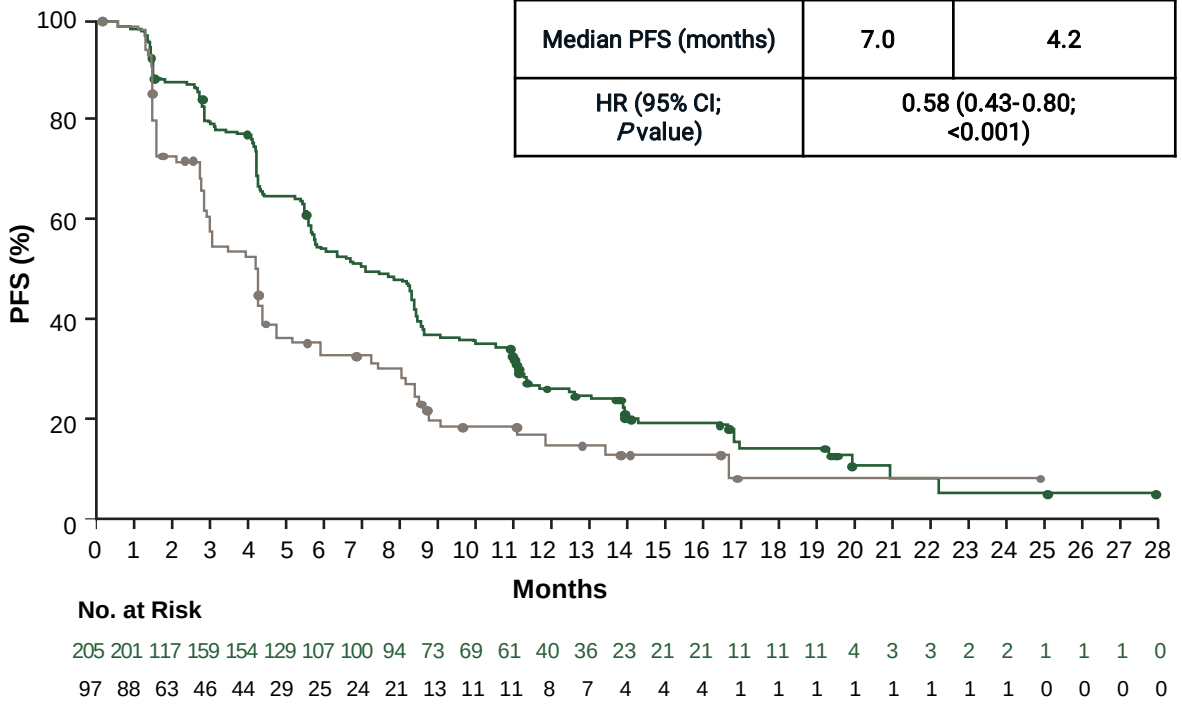
OlympiAD
*Efficacy Results**

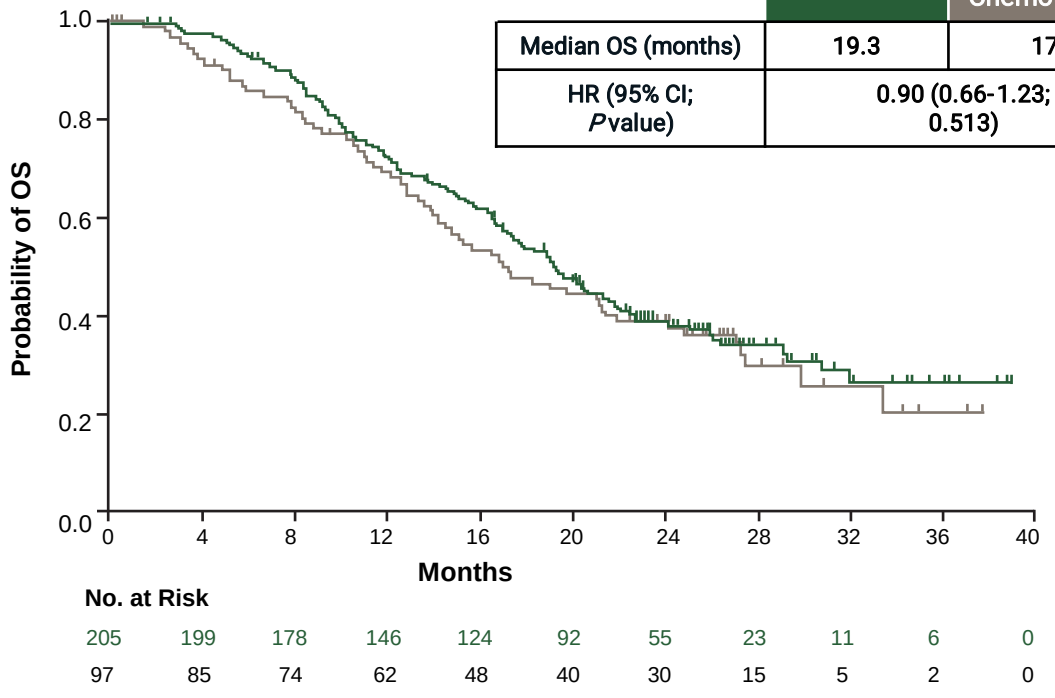
PFS[1]

	Olaparib	Standard Chemotherapy
Median PFS (months)	7.0	4.2
HR (95% CI; *P* value)	0.58 (0.43-0.80; <0.001)	



OS (Final Analysis)[2]

	Olaparib	Standard Chemotherapy
Median OS (months)	19.3	17.1
HR (95% CI; *P* value)	0.90 (0.66-1.23; 0.513)	



Single-agent olaparib provided a significant mPFS benefit over standard chemotherapy in patients with a germline BRCA1/2 mutation and HER2- MBC; however, no statistically significant improvement was observed in mOS.

*Data cut-off: Primary analysis – December 9, 2016; final OS analysis – September 25, 2017.

Clinical Trial Identification: NCT02000622

Abbreviations: BRCA1/2=Breast Cancer Susceptibility Genes 1 or 2; CI=Confidence Interval; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hazard Ratio; MBC=Metastatic Breast Cancer; mOS= Median Overall Survival; mPFS=Median Progression-Free Survival; OS=Overall Survival; PFS=Progression-Free Survival;

References: 1. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *NEJM.* 2017;377(6):523-533. Erratum in: *NEJM.* 2017;377(17):1700. 2. Robson ME, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability results: olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Ann Oncol.* 2019;30(4):558-566.

OlympiAD
*Safety Results**

AEs ≥20% in either arm, n (%)[a]	Olaparib (n=205)		Standard Therapy (n=91)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AEs	200 (97.6)	78 (38.0)	87 (95.6)	45 (49.5)
Nausea	119 (58.0)	0	32 (35.2)	1 (1.1)
Anemia	82 (40.0)	33 (16.1)	24 (26.4)	4 (4.4)
Neutropenia	56 (27.3)	19 (9.3)	45 (49.5)	24 (26.4)
Vomiting	66 (32.2)	0	14 (15.4)	1 (1.1)
Fatigue	61 (29.8)	7 (3.4)	22 (24.2)	1 (1.1)
Diarrhea	42 (20.5)	1 (0.5)	20 (22.0)	0
Headache	42 (20.5)	2 (1.0)	14 (15.4)	2 (2.2)
Decreased WBC	33 (16.1)	7 (3.4)	19 (20.9)	9 (9.9)
PPE	1 (0.5)	0	19 (20.9)	2 (2.2)

Warnings & Precautions

Olaparib can cause myelodysplastic syndrome/acute myeloid leukemia, pneumonitis, and embryo-fetal toxicity. For more information, please refer to the full US prescribing information at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208558s009lbl.pdf.

In the olaparib arm, the most common Any Grade AEs were nausea, anemia, neutropenia, vomiting, and fatigue.

*Data cut-off: Safety analysis – December 9, 2016; updated safety analysis – September 25, 2017.
Clinical Trial Identification: NCT02000622
[a]AEs of any cause; MedDRA-preferred terms are grouped for anemia (anemia, decreased Hb level, decreased hematocrit, decreased red blood cell count, and erythropenia) and neutropenia (febrile neutropenia, granulocytopenia, decreased granulocyte count, neutropenia, neutropenic sepsis, decreased neutrophil count, and neutropenic infection).
Abbreviations: AE=Adverse Event; Hb=Hemoglobin; MedDRA=Medical Dictionary for Regulatory Activities; PPE=Palmar Plantar Erythrodysesthesia; WBC=White Blood Cells.
Reference: 1. Robson ME, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability results: olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Ann Oncol.* 2019;30(4):558-566.

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EMBRACA
Study Design

Multicenter, open-label, randomized, controlled phase 3 study of talazoparib[1-3]

Key Eligibility Criteria

- Patients ≥18 years of age with HER2- ABC
- Deleterious or suspected deleterious germline *BRCA1/2* mutation
- Previous treatment with a taxane and/or an anthracycline[a]
- Prior hormone therapies for HR+ BC
- Patients with CNS metastases[b]
- ≤3 prior cytotoxic regimens for ABC
- ECOG PS: 0-1

2:1 Randomization (N=431)

- **Talazoparib 1 mg QD (n=287)**
- **Standard Chemotherapy[b] (capecitabine, eribulin mesylate, vinorelbine) (n=144)**

Primary Endpoint

- *BICR-assessed PFS*

Secondary Endpoints

- *OS, ORR, CBR, DoR, safety and PROs*

Stratification Factors

- *Previous cytotoxic CT for advanced disease (0 vs. 1-3)*
- *HR status (triple negative vs. HR+)*
- *History of CNS metastases (yes vs. no)*

Clinical Trial Identification: NCT01945775

[a]Disease-free interval of at least 6 months after the last dose.

[b]Completed definitive local treatment, stable CNS lesions on repeat brain imaging, and receiving low/no glucocorticoids.

Abbreviations: ABC=Advanced Breast Cancer; BC=Breast Cancer; BICR=Blinded Independent Central Review; BID=Twice Daily; BRCA1/2=Breast Cancer Susceptibility Genes 1 or 2; CBR=Clinical Benefit Rate; CNS=Central Nervous System; CT=Chemotherapy; DoR=Duration of Response; ECOG PS=Eastern Cooperative Oncology Group Performance Status; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; ORR=Objective Response Rate; OS=Overall Survival; PFS=Progression-Free Survival; PRO=Patient-Reported Outcome.

References: 1. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *NEJM*. 2018;379(8):753-763. 2. Rugo HS, Ettl J, Hurvitz SA, et al. Outcomes in clinically relevant patient subgroups from the EMBRACA study: talazoparib vs physician's choice standard-of-care chemotherapy. *JNCI Cancer Spectr*. 2020;4(1):pkz085. 3. Hurvitz SA, Gonçalves A, Rugo HS, et al. Talazoparib in patients with a germline BRCA-mutated advanced breast cancer: detailed safety analyses from the phase III EMBRACA trial. *Oncologist*. 2020;25(3):e439-e450.

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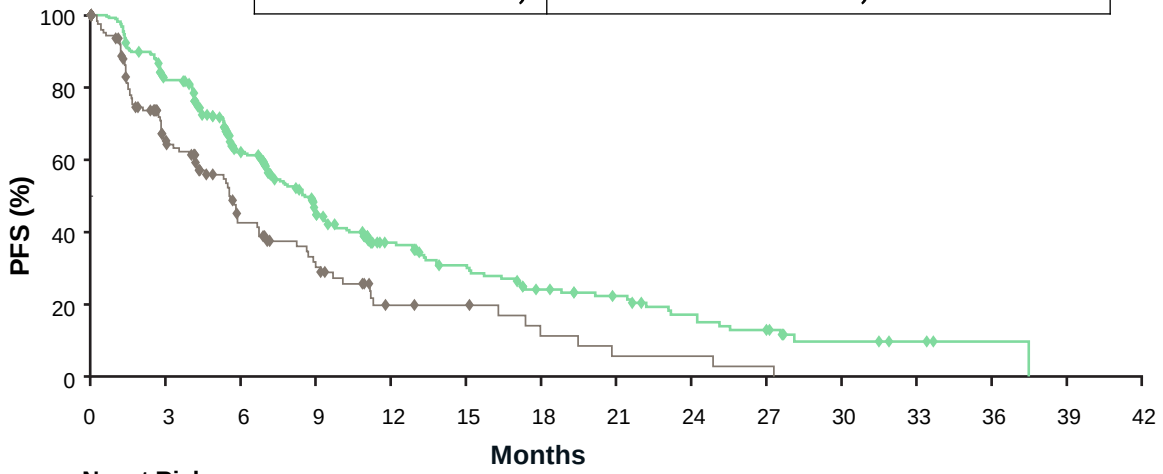
EMBRACA
Efficacy Results

PFS[a,1]

	Talazoparib	Standard Chemotherapy
Median PFS (months)	8.6	5.6
HR (95% CI; *P* value)	0.54 (0.41-0.71; <0.001)	

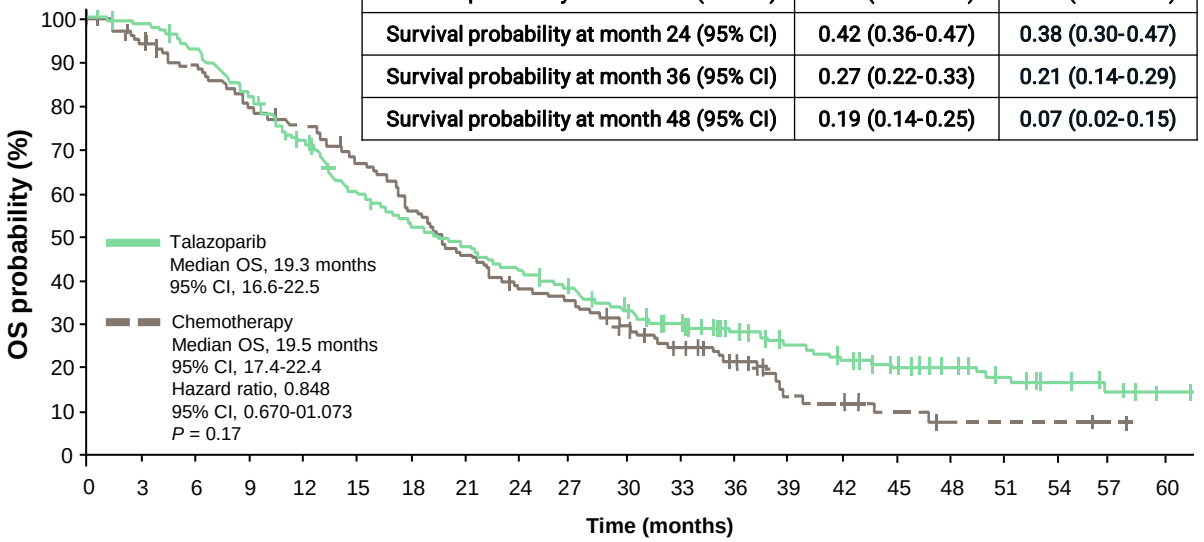


No. at Risk

287	229	148	91	55	42	29	23	16	12	5	3	1	0	0
144	68	34	22	9	8	4	2	2	1	0	0	0	0	0

Overall Survival[b,2]

	Talazoparib	Standard Chemotherapy
Survival probability at month 12 (95% CI)	0.71 (0.66-0.76)	0.74 (0.66-0.81)
Survival probability at month 24 (95% CI)	0.42 (0.36-0.47)	0.38 (0.30-0.47)
Survival probability at month 36 (95% CI)	0.27 (0.22-0.33)	0.21 (0.14-0.29)
Survival probability at month 48 (95% CI)	0.19 (0.14-0.25)	0.07 (0.02-0.15)



No. at Risk

287	280	264	232	199	163	143	128	113	101	85	68	54	41	35	27	20	15	9	6	2
287	280	264	232	96	86	71	58	48	44	34	25	18	8	7	4	2	2	2	1	0

Single-agent talazoparib provided a significant PFS benefit over standard chemotherapy for patients with a deleterious BRCA1/2 germline mutation and HER2- ABC; however, talazoparib did not significantly improve OS over standard chemotherapy

Clinical Trial Identification: NCT01945775

[a]Primary endpoint was met at the primary analysis (data cut-off: September 15, 2017). [b]Data cut-off: September 30, 2019

Abbreviations: ABC=Advanced Breast Cancer; BRCA1/2=Breast Cancer Susceptibility Genes 1 or 2; CI=Confidence Interval; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hazard Ratio; OS=Overall Survival; PFS=Progression-Free Survival.

References: 1. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *NEJM.* 2018;379(8):753-763. 2. Litton JK, Hurvitz SA, Mina LA, et al. Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial. *Ann Oncol.* 2020 Nov;31(11):1526-1535.

EMBRACA
*Safety Results**

TEAEs ≥20% in either arm, %[a]	Talazoparib (n=286)		Standard Therapy (n=126)	
	Any Grade	Grade 3+4	Any Grade	Grade 3+4
Fatigue	62.2	3.1	50.1	4.8
Anemia[a]	52.8	39.2	18.2	4.8
Nausea	48.5	0.3	46.9	1.6
Neutropenia[b]	34.5	20.9	42.8	34.9
Thrombocytopenia[c]	26.9	14.7	7.2	1.6
Alopecia	25.1	-	27.7	-
Vomiting	24.7	2.4	23.0	1.6

Warnings & Precautions

Talazoparib can cause myelodysplastic syndrome/acute myeloid leukemia, myelosuppression, and embryo-fetal toxicity. For more information, please refer to the full US prescribing information at https://labeling.pfizer.com/ShowLabeling.aspx?id=11046.

In the talazoparib arm, the most common Any Grade AEs were fatigue, anemia, nausea, neutropenia, and thrombocytopenia.

*Data cut-off: Safety analysis – September 15, 2017.
Clinical Trial Identification: NCT01945775
AEs were characterized and graded according to NCI-CTCAE – Grade 1: (<LLN to 1.5 x 10^9/L), Grade 2: (<1.5 to 1.0 x 10^9/L), Grade 3: (<1.0 to 0.5 x 10^9/L), Grade 4: (<0.5 x 10^9/L).
[a]Anemia includes anemia, decreased hemoglobin, decreased hematocrit.
[b]Neutropenia includes neutropenia, decreased neutrophil count.
[c]Thrombocytopenia includes thrombocytopenia, platelet count decreased.
Abbreviations: AE=Adverse Event; LLN=Lower Limit of Normal; NCI-CTCAE: US National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE=Treatment-Emergent Adverse Event.
Reference: Hurvitz SA, Gonçalves A, Rugo HS, et al. Talazoparib in patients with a germline BRCA-mutated advanced breast cancer: detailed safety analyses from the phase III EMBRACA trial. *Oncologist.* 2020;25(3):e439-e450.

LOXO@Lilly

Summary (PARPi)

01

PARP inhibitors demonstrated a significant PFS benefit as a monotherapy over standard chemotherapy for patients with HER2- ABC or MBC and a deleterious or suspected deleterious BRCA1/2 germline mutation.

02

Anemia, nausea, neutropenia, and fatigue were among the most common any grade adverse events in both the OlympiAD and EMBRACA studies.

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Abbreviations:
ABC=Advanced Breast Cancer; BRCA1/2=Breast Cancer Gene 1/2; HER2=Human Epidermal Growth Factor Receptor 2; MBC=Metastatic Breast Cancer; PARP=Poly-(ADP-Ribose) Polymerase; PARPi=Poly-(ADP-Ribose) Polymerase Inhibitor; PFS=Progression-Free Survival.

LOXO@Lilly

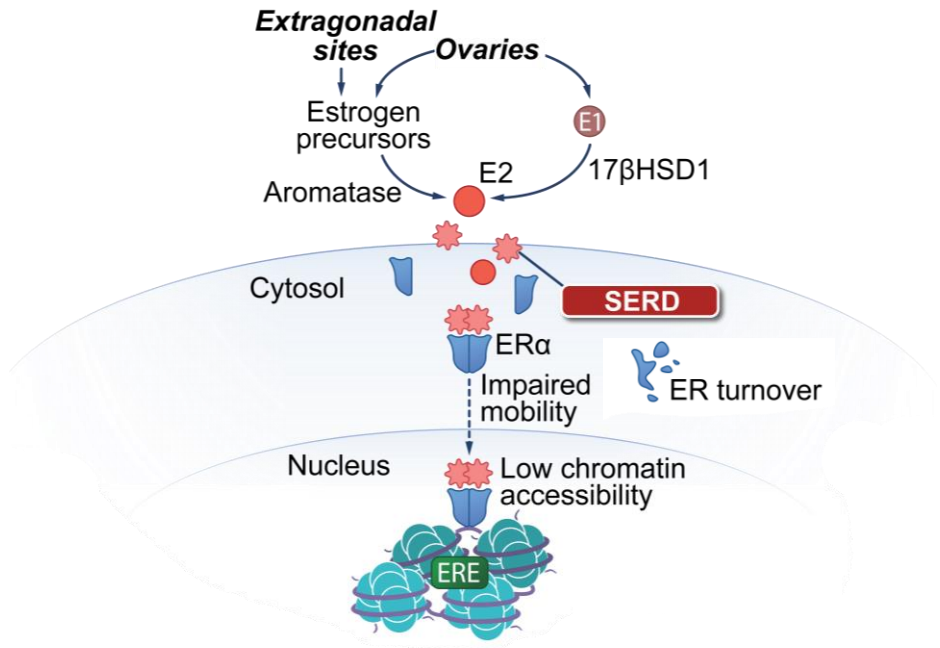
Selective Estrogen Receptor Modulators/Degraders (SERMs/SERDs): An Overview

SERMs/SERDs: Role in Cancer

Selective estrogen receptor modulators (SERMs) and selective estrogen receptor degraders (SERDs) are classes of endocrine therapy (ET) that bind to the estrogen receptor (ER). SERMs bind to ER and form an inactive ER complex while SERDs trigger ER degradation, limiting the ER's intranuclear mobility and suppressing its transcriptional activity[1-3]

- Estrogen signaling plays an important role in organ development and growth[1]
- In certain cancers, abnormal estrogen signaling via the estrogen receptor is a key component of tumor growth[1]
- Suppression of estrogen signaling by ET is one of the treatment options for patients with HR+ cancers[1,2]
- 25%-50% of patients with HR+ breast cancers either have de novo endocrine resistance at first use, or develop endocrine resistance within 2 years after initial response, often presenting with more aggressive and metastatic disease[1,4-5]
    - Mutations in *ESR1* (gene encoding ERα), found in ~20% of recurrent ER+ breast cancers, are frequent drivers of resistance in ER+ MBC and are usually acquired following long-term treatment with AIs or tamoxifen[2]
    - Fulvestrant (a SERD) has limited activity against *ESR1* aberrations frequently acquired during prior AI treatment[6]
- Elacestrant is a novel, nonsteroidal, oral estrogen receptor antagonist (SERM/SERD) that degrades ERα and inhibits estradiol-dependent ER-directed gene transcription and tumor growth[7]

SERDs reduce the ability of SERD-bound ER to translocate to the nucleus and inhibit an open chromatin conformation to facilitate transcription of ER-regulated genes[2,8]



Abbreviations: 17βHSD1, 17β-hydroxysteroid dehydrogenase 1; E2, estradiol; ER, estrogen receptor; ERE, estrogen response element; ESR1, estrogen receptor 1 gene; MBC, metastatic breast cancer.

References: 1. Patel HK, Bihani T. Selective estrogen receptor modulators (SERMs) and selective estrogen receptor degraders (SERDs) in cancer treatment. *Pharmacol Ther.* 2018;186:1-24. 2. Hanker AB, Sudhan DR, Arteaga CL. *Cancer Cell* 2020;37:496-513. 3. Nardone A, Weir H, Delpuech O, et al. The oral selective oestrogen receptor degrader (SERD) AZD9496 is comparable to fulvestrant in antagonising ER and circumventing endocrine resistance. *Br J Cancer.* 2019;120:331-339. 4. Sini V, Cinieri S, Conte P, et al. Endocrine therapy in post-menopausal women with metastatic breast cancer: From literature and guidelines to clinical practice. Crit Rev Oncol Hematol. 2016 Apr;100:57-68. 5. Clarke R, Tyson JJ, Dixon JM. Endocrine resistance in breast cancer--An overview and update. Mol Cell Endocrinol. 2015 Dec 15;418 Pt 3(0 3):220-34. 6. Brett JO, Spring LM, Bardia A, et al. ESR1 mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer. *Breast Cancer Res.* 2021;23(1):85. 7. Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. *J Clin Oncol.* 2022 Oct 1;40(28):3246-3256. 8. Barakat R, Oakley O, Kim H, et al. Extra-gonadal sites of estrogen biosynthesis and function. *BMB Rep.* 2016 Sep;49(9):488-96.

EMERALD
Study Design

International, multicenter, randomized, open-label, phase 3 study

Key Eligibility Criteria

- Postmenopausal women or men ≥18 years of age with ER-positive/HER2-negative ABC
- 1-2 lines of ET
- Required pretreatment with a CDK4/6 inhibitor
- ≤ 1 chemotherapy
- ECOG PS: 0-1

1:1 Randomization (N=694)

Elacestrant (400 mg/daily) **(n=239)**

Standard of care ET* **(n=238)**

Primary Endpoint

- *Investigator-assessed PFS (overall population and in patients with detectable ESR1 mutations)*

Secondary Endpoints

- *OS, ORR, duration of response, CBR, safety/tolerability*

Stratification Factors

- *ESR1 mutational status*
- *Presence of visceral metastases*
- *Previous treatment with fulvestrant*

*Per investigator's choice of fulvestrant, anastrozole, letrozole, or exemestane monotherapy dosed according to the labeling.

Clinical Trial Identification: NCT03778931.

Abbreviations: ABC=Advanced Breast Cancer; AI=Aromatase Inhibitor; CDK=Cyclin-dependent Kinase; ET=Endocrine Therapy;HER2=Human Epidermal Growth Factor Receptor 2; HR=hormone receptor; ORR=Objective Response Rate; OS=Overall Survival; PFS=Progression-Free Survival; SOC=Standard of Care.

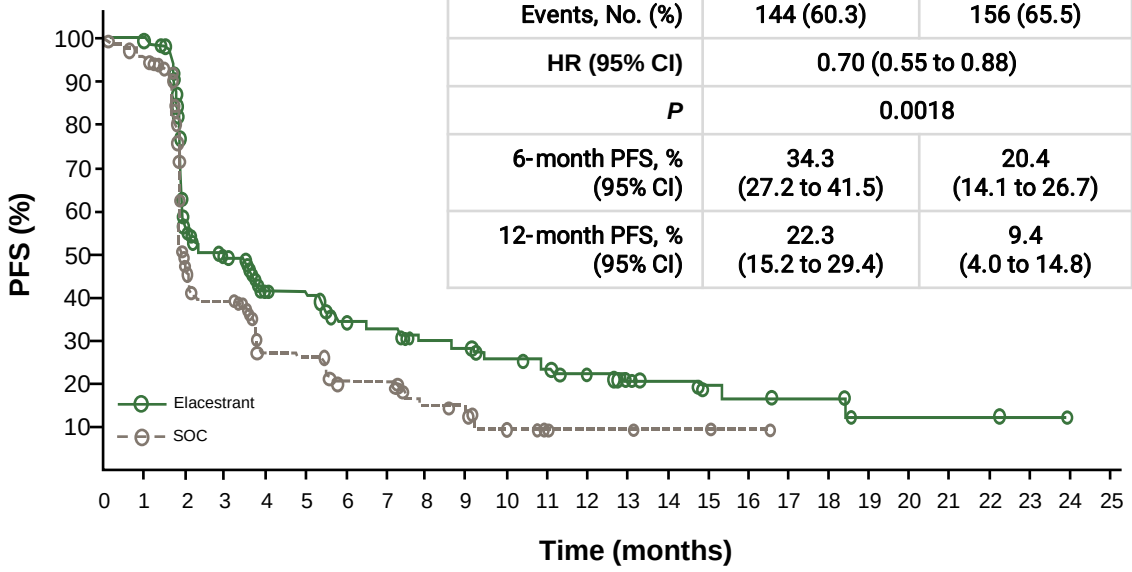
References: Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. *J Clin Oncol.* 2022;40(28):3246-3256.

EMERALD

*Efficacy Results**

PFS (in ALL patients)

	Elacestrant (n = 239)	SOC (n = 238)
Events, No. (%)	144 (60.3)	156 (65.5)
HR (95% CI)	0.70 (0.55 to 0.88)	
P	0.0018	
6-month PFS, % (95% CI)	34.3 (27.2 to 41.5)	20.4 (14.1 to 26.7)
12-month PFS, % (95% CI)	22.3 (15.2 to 29.4)	9.4 (4.0 to 14.8)

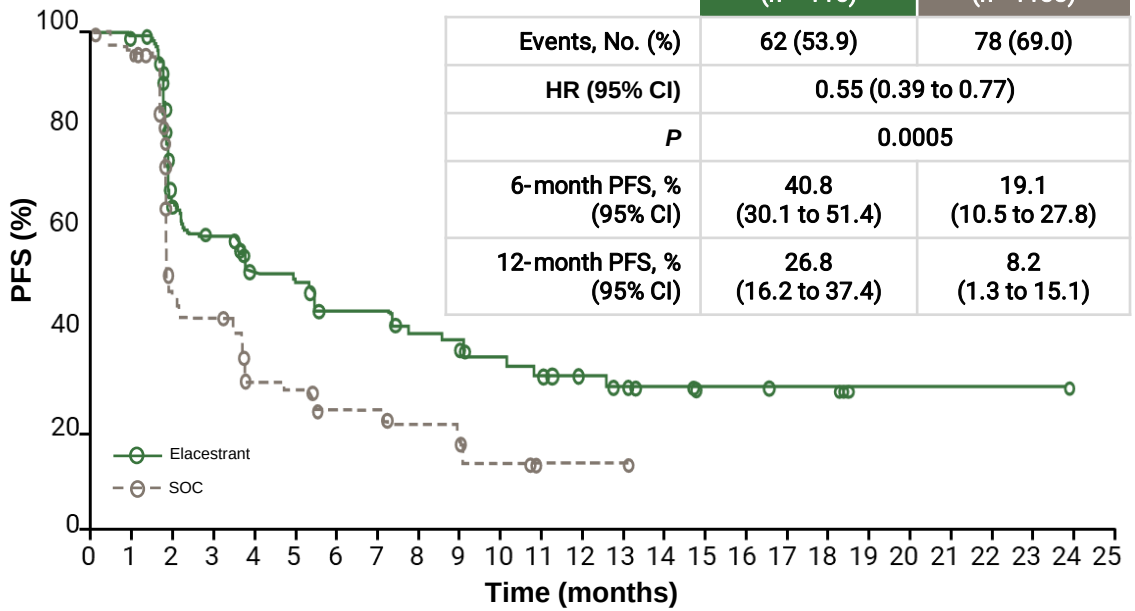


No. at risk

239	223	106	89	60	57	42	40	34	33	27	24	19	13	11	8	7	6	6	2	2	2	2	1	0
238	206	84	68	39	38	25	25	16	15	7	4	3	3	2	2	1	0							

PFS (patients with detectable *ESR1* mutation)

	Elacestrant (n = 115)	SOC (n =1138)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	0.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)



No. at risk

115	105	54	46	35	33	26	26	21	20	16	14	11	9	7	5	5	4	4	1	1	1	1	1	0
113	99	39	34	19	18	12	12	9	9	4	1	1	1	0										

Elacestrant demonstrated a significant improvement in PFS versus SOC therapy in ER-positive, HER2-negative, advanced or metastatic breast cancer in the second- or third-line setting

*Data cut-off: September 6, 2021.

Clinical Trial Identification: NCT03778931.

Abbreviations: CI=Confidence Interval; HR=Hazard Ratio; PFS=Progression-Free Survival; SOC=standard of care.

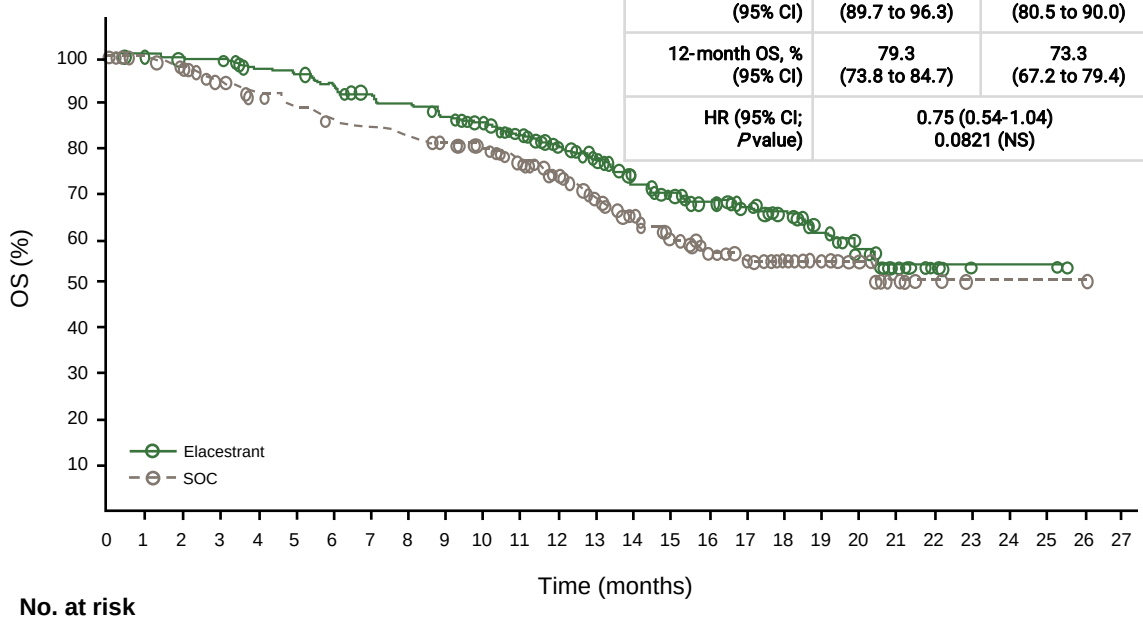
Reference: Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. *J Clin Oncol.* 2022;40(28):3246-3256.

EMERALD

*Efficacy Results**

Interim analysis overall survival (All patients)

	Elacestrant (n = 239)	SOC (n = 238)
6-month OS, % (95% CI)	93.0 (89.7 to 96.3)	85.2 (80.5 to 90.0)
12-month OS, % (95% CI)	79.3 (73.8 to 84.7)	73.3 (67.2 to 79.4)
HR (95% CI; *P* value)	0.75 (0.54-1.04) 0.0821 (NS)	

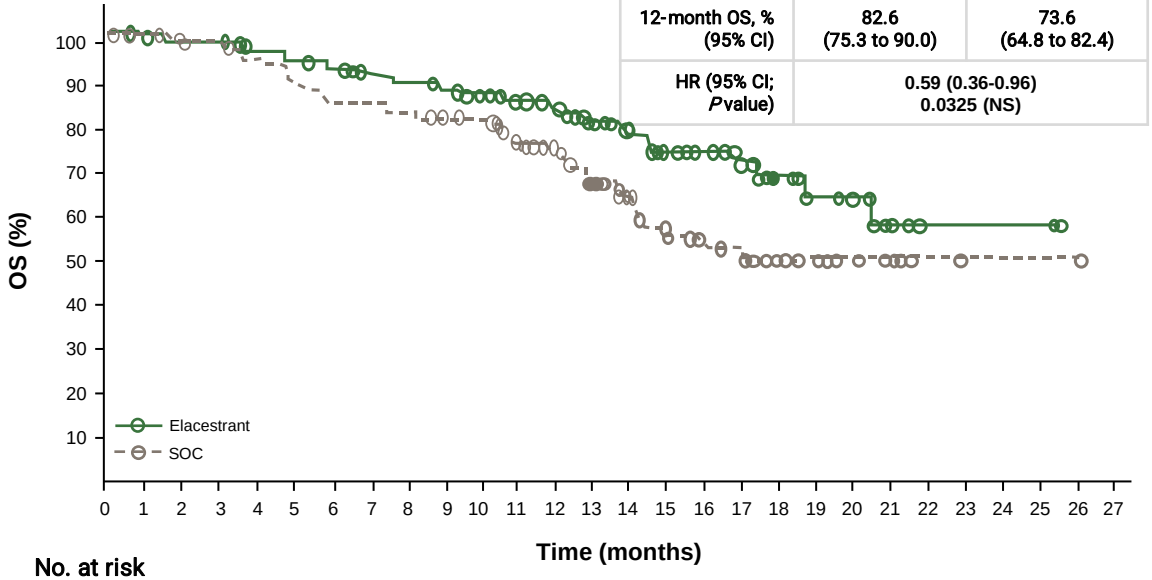


No. at risk

239	233	230	229	220	218	211	202	197	191	180	166	139	118	98	89	78	60	49	33	22	10	5	2	2	2	0
238	223	216	206	164	187	179	177	173	163	157	144	118	96	78	67	49	42	31	23	15	6	3	1	1	1	0

Interim analysis of overall survival (Patients with detectable *ESR1* mutation)

	Elacestrant (n = 115)	SOC (n = 113)
6-month OS, % (95% CI)	92.8 (88.0 to 97.6)	84.4 (77.3 to 91.4)
12-month OS, % (95% CI)	82.6 (75.3 to 90.0)	73.6 (64.8 to 82.4)
HR (95% CI; *P* value)	0.59 (0.36-0.96) 0.0325 (NS)	



No. at risk

115	112	111	111	105	103	101	95	93	90	86	80	68	55	45	40	36	25	17	13	11	4	2	2	2	2	0
113	106	101	101	96	90	86	86	84	79	77	68	56	44	33	27	22	19	14	10	6	4	2	1	1	1	0

The differences in overall survival in this interim analysis were not statistically significant on the basis of the allocated two-sided alpha level of 0.0001. The final OS results will be provided in the future when data are mature.

*Data cut-off: September 6, 2021.

Clinical Trial Identification: NCT03778931

Abbreviations: CI=Confidence Interval; HR=Hazard Ratio; NS=nonsignificant; OS=Overall Survival; SOC=standard of care.

Reference: Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. *J Clin Oncol.* 2022;40(28):3246-3256.

EMERALD

*Safety Results (Overall Population)**

AEs[a] ≥10% in either arm, n (%)	Elacestrant (n=237)		SOC (n=229)	
	Any Grade	Grade 3+4[b]	Any Grade	Grade 3+4
Any AEs	218 (92.0)	64 (27.0)	197 (86.0)	47 (20.5)
Nausea	83 (35.0)[c]	6 (2.5)	43 (18.8)	2 (0.9)
Fatigue	45 (19.0)	2 (0.8)	43 (18.8)	2 (0.9)
Vomiting	45 (19.0)[d]	2 (0.8)	19 (8.3)	0 (0.0)
Decreased appetite	35 (14.8)	2 (0.8)	21 (9.2)	1 (0.4)
Arthralgia	34 (14.3)	2 (0.8)	37 (16.2)	0 (0.0)
Diarrhea	33 (13.9)	0 (0.0)	23 (10.0)	2 (0.9)
Back pain	33 (13.9)	6 (2.5)	22 (9.6)	1 (0.4)
AST increased	31 (13.1)	4 (1.7)	28 (12.2)	2 (0.9)
Headache	29 (12.2)	4 (1.7)	26 (11.4)	0 (0.0)
Constipation	29 (12.2)	0 (0.0)	15 (6.6)	0 (0.0)
Hot flush	27 (11.4)	0 (0.0)	19 (8.3)	0 (0.0)
Dyspepsia	24 (10.1)	0 (0.0)	6 (2.6)	0 (0.0)
ALT increased	22 (9.3)	5 (2.1)	23 (10.0)	1 (0.4)

Warnings & Precautions

Elacestrant can cause dyslipidemia and embryo-fetal toxicity. For more information, please refer to the full US prescribing information at https://rxmenarinistemline.com/ORSERDU_elacestrant_Full_Prescribing_Information.pdf

Elacestrant exhibited manageable toxicity with most AEs of grade 1 or 2 severity. The most frequent AE was nausea and was of grade 3 severity in 2.5% of patients.

*Data cut-off: September 6, 2021.

Clinical Trial Identification: NCT03778931.

Abbreviations: AE=Adverse Event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; SOC=Standard of Care.

[a]Preferred terms were coded using the Medical Dictionary for Regulatory Activities version 23.0

[b]AE severity was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0.

[c]Grade 1 nausea, n=59 (24.9%); grade 2 nausea, n=18 (7.6%); grade 3 nausea, n=6 (2.5%); and no patients experienced grade 4 nausea. Percentages reflect maximum grade experienced.

[d]Grade 1 vomiting, n=36 (15.2%); grade 2 vomiting, n=7 (3.0%); grade 3 vomiting, n=2 (0.8%); and no patients experienced grade 4 vomiting. Percentages reflect maximum grade experienced.

Reference: Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. *J Clin Oncol.* 2022;40(28):3246-3256.

Summary

01 Targeted therapy has become an established treatment in recent years, and has demonstrated improved PFS, and in some cases improved OS, in patients with HR+, HER2- ABC or MBC.

02 CDK 4 & 6 inhibitors have been recognized as first- and second-line therapies and can improve PFS and OS in selected patients with HR+, HER2- MBC.

03 Biomarker-driven therapy is now a reality in HR+, HER2- MBC with PI3Ki, AKTi, PARPi, and SERDs showing clinical benefit in specific biomarker-selected populations.

LOXO@Lilly

Abbreviations: ABC=Advanced Breast Cancer; CDK=Cyclin-Dependent Kinase; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; MBC=Metastatic Breast Cancer; OS=Overall Survival; PARPi= Poly-(ADP-Ribose) Polymerase Inhibitor; PI3Ki=Phosphoinositide-3-Kinase Inhibitor; PFS=Progression-Free Survival; SERD=Selective Estrogen Receptor Degraders.