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

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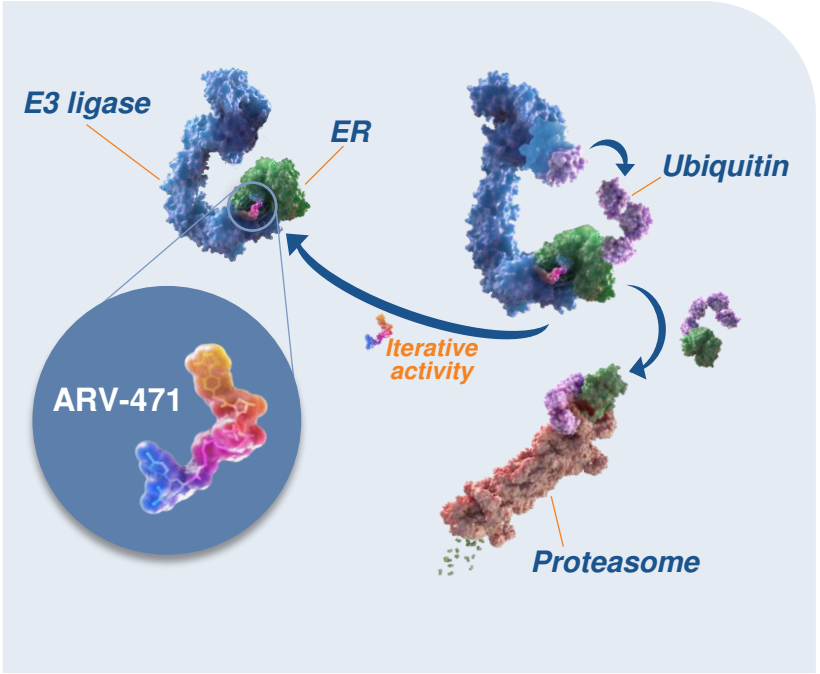
Background

- ARV-471 is a selective, orally administered PROTAC® protein degrader that targets wild-type and mutant ER[1]
- ARV-471 directly binds an E3 ubiquitin ligase and ER to trigger ubiquitination of ER and its subsequent proteasomal degradation
  - In contrast, SERDs indirectly recruit the ubiquitin-proteasome system, secondary to conformational changes and/or immobilization of ER[2]
- Limitations of the SERD fulvestrant include its intramuscular route of administration[3] and only 40%–50% ER protein degradation at its optimal dose[4,5]
- ARV-471 treatment yielded substantially greater ER degradation and tumor growth inhibition than fulvestrant in breast cancer xenograft models[1]



ER=estrogen receptor; PROTAC=PROteolysis TArgeting Chimera; SERD=selective estrogen receptor degrader

1. Flanagan, JJ, et al. *Cancer Research.* 2019;79(4 Suppl):P5-04.
2. Hanker AB, et al. *Cancer Cell.* 2020;37(4):496-513.
3. Nathan MR and Schmid P. *Oncol Ther.* 2017;5:17-29.
4. Kuter I, et al. *Breast Cancer Res Treat.* 2012;133(1):237-246.
5. Robertson JFR, et al. *Breast Cancer Res.* 2013;15(2).R18.

Phase 1/2 Study Design[a]

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

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

[a]ClinicalTrials.gov: NCT04072952

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

Phase 1 ARV-471 Dose Escalation Results[1]

Phase 1 dose escalation (Part A)

Treatment

- ARV-471 orally

Primary objective

- Evaluate the safety and tolerability of ARV-471 in order to estimate the MTD and select the RP2Ds

- As of September 30, 2021, 60 patients received ARV-471
  - Total daily doses ranged from 30–700 mg
- ARV-471 was well tolerated at all doses, with no DLTs or grade ≥4 TRAEs; most TRAEs were grade 1/2
- The CBR[a] was 40% (95% CI: 26–56) in 47 evaluable patients
- 3 patients had confirmed PRs
- Preliminary PK data showed dose-related increases for AUC_{24} and C_{max} from 30–500 mg daily doses
- At the 200-mg and 500-mg doses, mean exposure on day 15 exceeded the nonclinical efficacious range by >2-fold and >5-fold, respectively[2]
- ER degradation up to 89% was observed; median and mean ER degradation across dose levels was 67% and 64%, respectively

[a]Rate of confirmed complete response or partial response or stable disease ≥24 weeks; evaluable patients were enrolled ≥24 weeks prior to the data cutoff

AUC_{24}=area under the curve from 0 to 24 hours; CBR=clinical benefit rate; C_{max}=maximum plasma concentration; DLT=dose-limiting toxicity; ER=estrogen receptor; MTD=maximum tolerated dose; PK=pharmacokinetic; PR=partial response; RP2D=recommended phase 2 dose; TRAE=treatment-related adverse event

1. Hamilton E, et al. Presented at SABCS; Dec 7-10, 2021; Poster PD13-08. 2. Snyder LB, et al. Presented at AACR; April 10-15, 2021; Oral Presentation 44.

Phase 2 (VERITAC) Cohort Expansion Design

Phase 2 cohort expansion (Part B; VERITAC)

Key eligibility criteria

- Histologically or cytologically confirmed ER+ and HER2- advanced breast cancer
- Measurable or nonmeasurable disease per RECIST criteria v1.1
- ≥1 prior endocrine regimen (≥1 regimen for ≥6 months in the locally advanced or metastatic setting)
- ≥1 prior CDK4/6 inhibitor
- ≤1 prior chemotherapy regimen in the locally advanced or metastatic setting

ARV-471 200 mg orally QD[a] (n=35)

ARV-471 500 mg orally QD[a] (n=36)

Primary endpoint

- CBR (rate of confirmed CR or PR or SD ≥24 weeks)[b]

Secondary endpoints

- ORR, DOR, PFS, and OS
- AEs and laboratory abnormalities
- PK parameters

Exploratory endpoints

- *ESR1* mutational status
- ER protein levels

Data cutoff date for this analysis

- June 6, 2022

[a]Enrollment in the 200-mg QD cohort began before enrollment in the 500-mg QD cohort
[b]Analyzed in patients enrolled ≥24 weeks prior to the data cutoff
AE=adverse event; CBR=clinical benefit rate; CDK=cyclin-dependent kinase; CR=complete response; DOR=duration of response; ER=estrogen receptor; *ESR1*=estrogen receptor 1 gene; HER2=human epidermal growth factor receptor 2; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic; PR=partial response; QD=once daily; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease

Patient Baseline Characteristics (VERITAC)

Characteristic	Total (N=71)
Sex, n (%)	
Female	69 (97.2)
Median age, y (range)	60 (41–86)
ECOG PS, n (%)[a]	
0	47 (66.2)
1	23 (32.4)
Visceral disease, n (%)	39 (54.9)
Sites of metastasis, n (%)	
Bone	49 (69.0)
Liver	32 (45.1)
Lung	17 (23.9)
Other	5 (7.0)

Characteristic	Total (N=71)
Baseline *ESR1* status, n (%)[b]	
Mutant	41 (57.7)
Wild-type	25 (35.2)
Median no. of prior regimens (range)	
Any setting	4 (1–10)
Metastatic setting	3 (0–7)
Type of prior therapy, n (%)	
CDK4/6 inhibitor	71 (100)
Aromatase inhibitor	64 (90.1)
Fulvestrant	56 (78.9)
Chemotherapy	
Any setting	52 (73.2)
Metastatic setting	32 (45.1)

[a]Baseline ECOG PS status was unknown in 1 patient. [b]Baseline *ESR1* status was unknown or missing in 5 patients
CDK=cyclin-dependent kinase; ECOG PS=Eastern Cooperative Oncology Group performance status; *ESR1*=estrogen receptor 1 gene

Treatment-Emergent Adverse Event Summary (VERITAC)

n (%)	200 mg QD (n=35)	500 mg QD (n=36)	Total (N=71)
TEAEs			
Any grade	32 (91)	30 (83)	62 (87)
Grade 3/4	9 (26)	6 (17)	15 (21)
Grade 5[a]	1 (3)	0	1 (1)
Leading to discontinuation	1 (3)	2 (6)	3 (4)
Leading to dose reduction	0	3 (8)	3 (4)

- Dose reductions due to TEAEs
  - 500-mg QD cohort (to 400 mg QD)
    - ALT increased (n=1)
    - Neutropenia (n=1)
    - Fatigue (n=1)
- Discontinuations due to TEAEs
  - 200-mg QD cohort
    - QT prolongation (n=1)[b]
  - 500-mg QD cohort
    - ECG T-wave abnormality (n=1)[c]
    - Back pain/spinal cord compression (n=1)

[a]Acute respiratory failure in the setting of disease progression and unrelated to ARV-471 treatment
[b]Patient had QT prolongation at baseline, received a concomitant QT-prolonging drug during ARV-471 treatment, and had hypokalemia
[c]Patient had ECG T-wave abnormality at baseline
ALT=alanine aminotransferase; ECG=electrocardiogram; QD=once daily; TEAE=treatment-emergent adverse event

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

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

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

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

	200 mg QD (n=35)	500 mg QD (n=36)	Total (N=71)
CBR, % (95% CI)	37.1 (21.5–55.1)	38.9 (23.1–56.5)	38.0 (26.8–50.3)

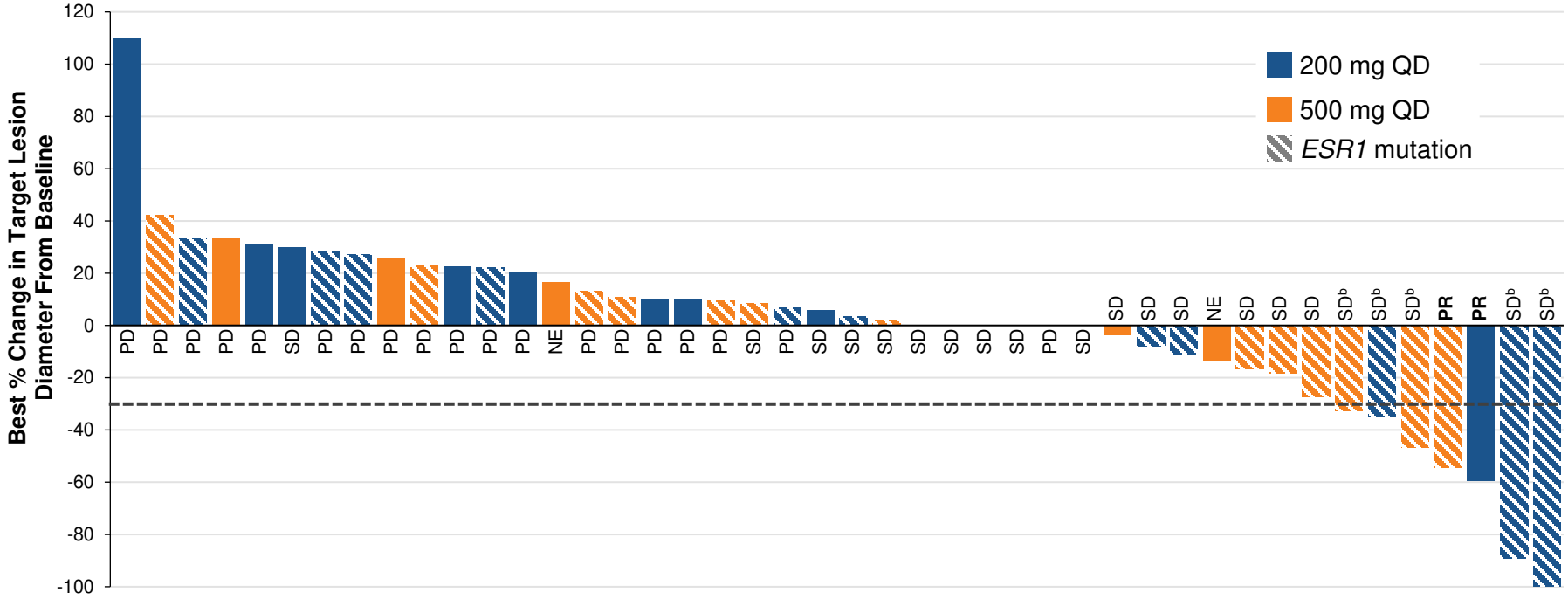
[a]Rate of confirmed complete response or partial response or stable disease ≥24 weeks
CBR=clinical benefit rate; QD=once daily

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

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

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

Tumor Response[a] (VERITAC)



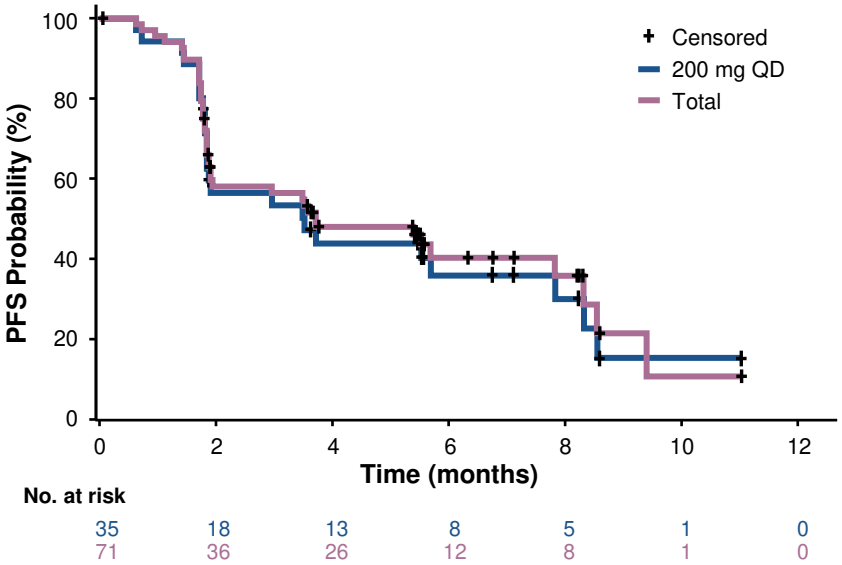
[a]Includes patients with measurable disease (n=44); 1 patient with measurable disease at baseline and PD as best overall response was excluded due to lack of complete set of target lesion measurements on-study

[b]Patient had an unconfirmed partial response

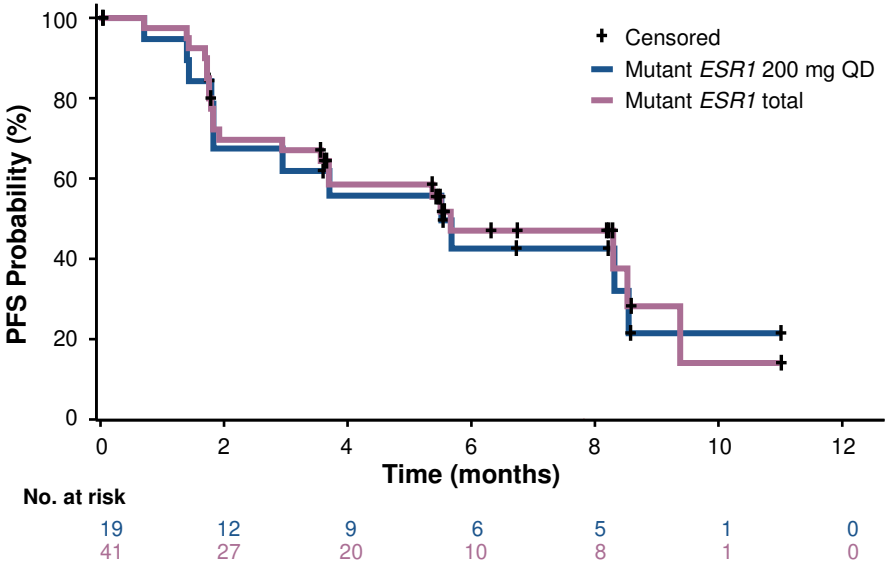
ESR1=estrogen receptor 1 gene; NE=not evaluable due to missing data for best overall response; PD=progressive disease; PR=confirmed partial response; QD=once daily; SD=stable disease

Progression-Free Survival[a] (VERITAC)

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



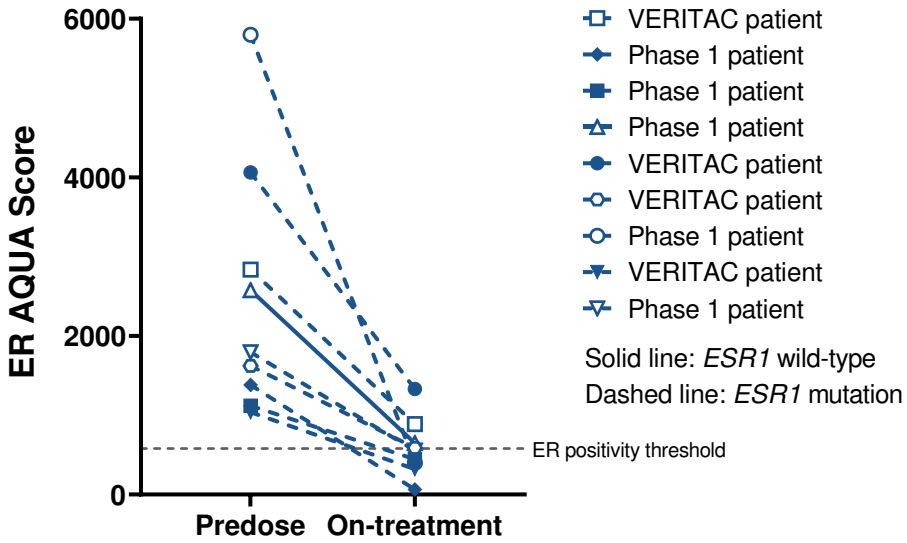
	Mutant *ESR1*	
	200 mg QD (n=19)	Total (n=41)
Events, n (%)	12 (63.2)	22 (53.7)
mPFS, mo (95% CI)	5.5 (1.8–8.5)	5.7 (3.6–9.4)



[a]Limited follow-up in 500-mg QD cohort led to ≥50% of patients censored for PFS (curve not shown)

ESR1=estrogen receptor 1 gene; mPFS=median progression-free survival; PFS=progression-free survival; QD=once daily

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



- Median ER degradation was 69% (range: 28%–95%)
- Mean ER degradation was 71%

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

Conclusions

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

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

Phase 3 VERITAC-2 Trial

Key eligibility criteria

- Women or men aged ≥18 years
- Confirmed ER+/HER2- advanced breast cancer
- 1 line of CDK4/6 inhibitor therapy in combination with endocrine therapy
- ≤1 additional endocrine therapy
- Most recent endocrine treatment given for ≥6 months prior to disease progression
- No prior fulvestrant
- No prior chemotherapy for locally advanced/metastatic disease
- Radiological progression during or after the last line of therapy

RANDOMIZE 1:1

Treatment (N=560)

ARV-471
200 mg orally once daily

Fulvestrant
500 mg intramuscularly days 1 and 15 of cycle 1 and day 1 of subsequent cycles

Stratification factors
- *ESR1* mutant (yes vs no)
- Visceral disease (yes vs no)

Primary endpoint
- PFS by BICR in
  - ITT population
  - *ESR1* mutant population

Secondary endpoints include:
- OS, ORR, DOR, and CBR[a]
- AEs
- QoL measurements

[a]Rate of confirmed complete response or partial response or stable disease ≥24 weeks

AE=adverse event; BICR=blinded independent central review; CBR=clinical benefit rate; CDK=cyclin-dependent kinase; DOR=duration of response; ER=estrogen receptor; *ESR1*=estrogen receptor 1 gene; HER2=human epidermal growth factor receptor 2; ITT=intention to treat; ORR=overall response rate; OS=overall survival; QoL=quality of life; PFS=progression-free survival

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Plain Language Summary

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