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ARV-471: Phase 2 VERITAC Trial Results

San Antonio Breast Cancer Symposium
December 8, 2022

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Introduction

ARV-471: Potential best-in-class estrogen receptor-targeting therapy

Continued signals of efficacy across the Phase 1/2 trial in a patient population with **100% pretreatment with CDK4/6 inhibitors**

- To our knowledge, this is the **most heavily pre-treated patient population evaluated** with an ER-targeted therapy to date, and is expected to have highly ER-independent disease
- In VERITAC: 100% prior CDK4/6i, 79% prior fulvestrant, and 73% prior chemo (45% in the metastatic setting)

	Clinical Benefit Rate (n)[a]
December 2020 (Phase 1 dose escalation)	42% (5 of 12)
December 2021 (Phase 1 dose escalation)	40% (19 of 47)
December 2022 (Phase 2 cohort expansion [VERITAC])	38% (27 of 71)

In VERITAC, favorable tolerability at both 200 mg qd and 500 mg qd

- No single TRAE in more than ~20% of patients
- In 35 patients treated at 200mg (RP3D), no dose reductions and only 1 discontinuation
- In this expansion cohort, no signal for bradycardia or visual disturbance

Expect to begin two Ph 3 pivotal studies and in multiple ongoing combination and monotherapy studies with the potential position ARV-471 as the ER therapy of choice across ER+/HER2- breast cancer

- 2L monotherapy Ph 3 to test patients with both ESR1-mutant tumors and all-comers (4Q 2022)
- 1L combination Ph3 with palbociclib in patients without prior CDK4/6i (1Q 2023)

[a]Rate of confirmed complete response or partial response or stable disease ≥24 weeks
CBR=clinical benefit rate; ER=estrogen receptor; *ESR1*=estrogen receptor 1 gene; PFS=progression-free survival; TRAE, treatment-related adverse events; RP3D, recommended Phase 3 dose; CDK, cyclin-dependent kinase

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ARV-471: Potential to be the endocrine backbone of choice for ER+/HER2- breast cancer treatment

Potential Future US ER+/HER2- Breast Cancer Treatment Paradigm with ARV-471

	Adjuvant (Post-Surgical) Breast Cancer (~160K)*	Metastatic Breast Cancer (~50K*)	
		First Line	Second/Third Line
Endocrine Backbone	***Potential future state:* ARV-471** *Designed to be an oral, high-potency ER degrader with favorable safety profile*		
Add-on therapies		CDK4/6 and other targeted inhibitors	mTOR inhibitors or PIK3 inhibitors
Opportunity for ARV-471	**Expansion**	**Near-term**	

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*U.S. incident population per year from SEER database
CDK: cyclin-dependent kinases, Pi3K: phosphoinositide 3-kinase; mTOR: mammalian target of rapamycin

Studies with SERDs or ARV-471 Include a Wide Range of Prior Therapies

VERITAC has most prior therapies among key studies

		CDK4/6 inhibitor	Fulvestrant	Chemotherapy in advanced / metastatic setting
PALOMA-3[1]	**Phase 3 study of palbociclib plus fulvestrant vs placebo plus fulvestrant (N=521)**	0	0	34%‡
acelERA[2]	**Phase 2 study of giredestrant vs SOC† (N=303)**	42%*	19%*	32%
SERENA-2[3]	**Phase 2 study of camizestrant vs fulvestrant (N=240)**	50%	0	19%
AMEERA-3[2]	**Phase 2 study of amcenestrant vs SOC† (N=290)**	79%*,‡	10%*,‡	11%‡
VERONICA[4]	**Phase 2 study of venetoclax plus fulvestrant vs fulvestrant (N=103)**	**100%**	**0**	**0**
EMERALD[5]	**Phase 3 study of elacestrant vs SOC† (N=477)**	**100%**	**30%**	**22%**
VERITAC	**Phase 2 expansion cohorts of ARV-471 (N=71)**	**100%**	**79%**	**45%**

Expected Efficacy

Expected Resistance

[1]Lancet Oncol 2016. [2]ESMO 2022. [3]San Antonio Breast Cancer Symposium 2022. [4]Clin Cancer Res 2022..[5]J Clin Oncol 2022.
*Advanced/metastatic setting. †Physician's choice of fulvestrant or an aromatase inhibitor; tamoxifen also permitted in AMEERA-3. SOC=standard of care
‡Published data, manually calculated for overall population

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ARV-471: VERITAC Phase 2 Detailed Results

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 non-measurable 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

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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

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

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

- CBR consistent with Phase 1 dose escalation data
  - Phase 1: 40% in all patients, 50% in patients with *ESR1*-mutant tumors
- Patients with WT ESR1 (n=25) exhibited CBR rate of 20%

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

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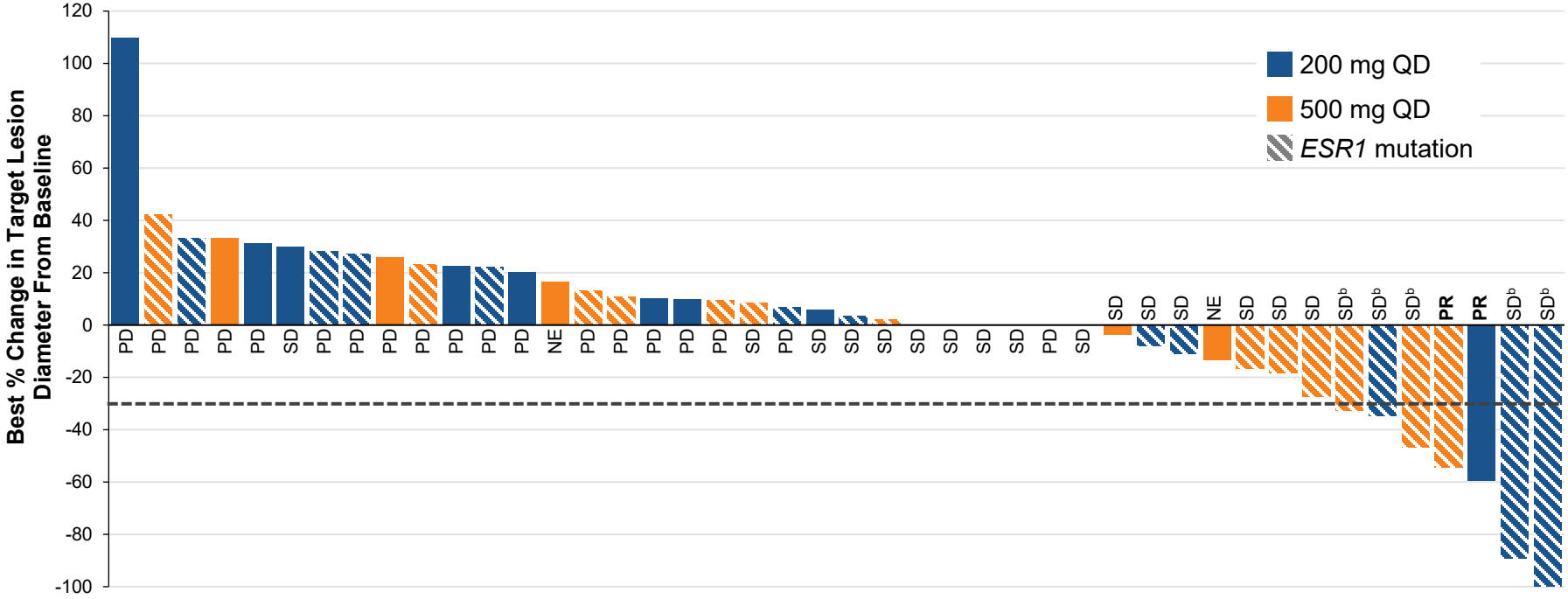
Tumor Response[a] (VERITAC)



[a]Includes patients with measurable disease (n=44); 1 patient with measurable disease at baseline and PD as best overall response was excluded due to lack of complete set of target lesion measurements on-study
[b]Patient had an unconfirmed partial response
ESR1=estrogen receptor 1 gene; NE=not evaluable due to missing data for best overall response; PD=progressive disease; PR=confirmed partial response; QD=once daily; SD=stable disease

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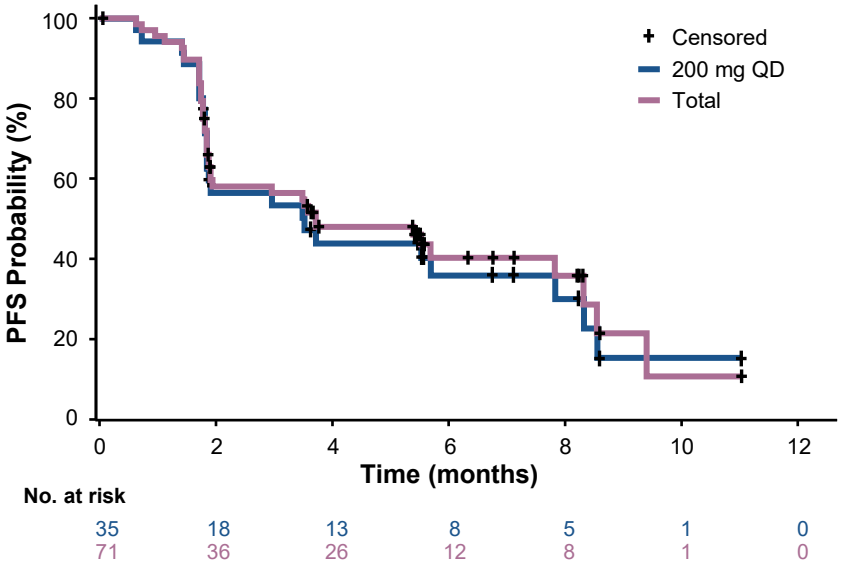
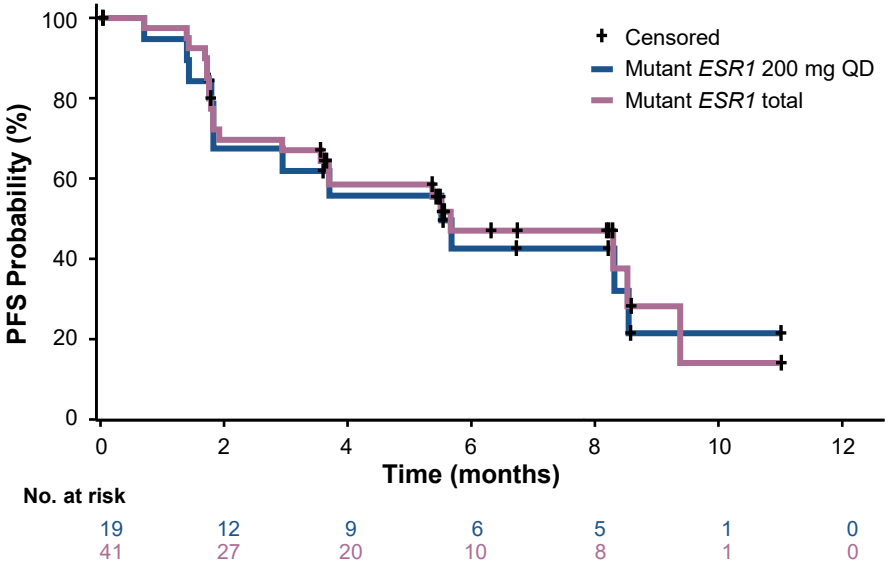
Progression-Free Survival[a] (VERITAC)

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



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



[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

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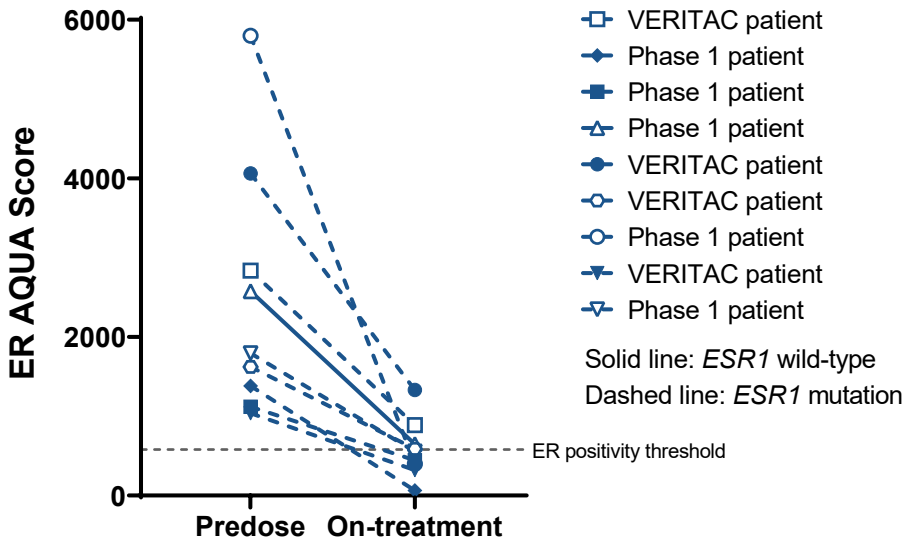
ER Degradation[a] With 200 mg QD ARV-471 (Phase 1/VERITAC)



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

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

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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)

[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

- 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)

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

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

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

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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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VERITAC Phase 2 Subset Results in Population Similar to the Target Phase 3 Eligibility Criteria Reinforces Our Belief for Potential Best-in-Class Profile

- **The Ph3 2L+ monotherapy trial for ARV-471** (VERITAC-2) will:
  - **Include** prior CDK 4/6
  - **Exclude** patients with prior fulvestrant or prior chemotherapy in the metastatic setting
- 8 patients in the VERITAC Phase 2 Expansion Cohort* did not have prior fulvestrant or prior chemotherapy in the metastatic setting (consistent with Phase 3 trial design):
  - CBR was **62.5%** (5 of 8) in these patients, vs. **38%** (27 of 71) in the ITT population
  - 3 of the 8 patients discontinued as of November*; the **5 continuing on therapy had durations of 8-14 months**

VERITAC Ph 2 Results

		Prior CDK4/6 inhibitor	Prior Fulvestrant	Prior Chemotherapy in metastatic setting	CBR	PFS
ITT	(n=71)	100%	78.9%	45.1%	38.0%	3.7 months
ITT ESR1m	(n=41)				51.2%	5.7 months
No prior fulvestrant or chemo*	(n=8)†	100%	**0%**	**0%**	**62.5%**	NR*

†All patients in the subset had ESR1 mutations
*Post-hoc analysis November 2022. Median PFS not reached as of November 2022

Conclusions

Continued efficacy and favorable tolerability put ARV-471 on a path to two pivotal studies beginning soon

Efficacy

- ARV-471 demonstrates strong CBR and mPFS in heavily treatment-resistant patients
- Activity in this difficult to treat population illustrates the potential of PROTAC technology

Tolerability

- Favorable tolerability profile at 200 and 500 mg qd
- At 200 mg phase 3 dose, no dose reductions and one discontinuation
- ARV-471's tolerability is well suited for development across the disease continuum

Initiating Ph 3 trials

- Monotherapy 2L Ph 3 in less treatment-experienced patients (Q4 2022)
  - Trial designed to address role in both *ESR1*mut and all-comers
- Palbo combo 1L Ph 3 in patients with ER dependent tumors (Q1 2023)
- Broader development initiated with other combos and in early breast cancer

ARV-471 is an investigational compound. Its safety and efficacy has not been established
[a]Rate of confirmed complete response or partial response or stable disease ≥24 weeks
CBR=clinical benefit rate; ER=estrogen receptor; *ESR1*=estrogen receptor 1 gene; PFS=progression-free survival

VERITAC data confirm ARV-471 has the potential to be a best-in-class ER-targeting therapy

✓ 2020: Phase 1 PoC	Validated PROTAC protein degrader
✓ 2021: Phase 1 Readout	Validated the evaluation of ARV-471 as a potential treatment for metastatic breast cancer
✓ 2022: Initiate Phase 1 in Japanese patients	Phase 1 trial in Japan to enable global pathway
✓ 2022: Planned initiation of TACTIVE-U, TACTIVE-E	Combination trials with multiple targeted therapies - on track to add additional agents to establish potential for ARV-471 as backbone therapy of choice
✓ 2022: Planned initiation of TACTIVE-N	Designed to evaluate safety and clinical activity in early breast cancer (e.g., neo-adjuvant)
✓ 2022: Phase 2 Readout	Continued efficacy signals and favorable tolerability profile support advancement to Phase 3 registrational studies
2022: Dose patients in the VERITAC-2 Ph 3 Trial (2L+ monotherapy)	First site has been initiated

Next milestone: Phase 3 registrational study (1L)

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Thank you