



ARV-471: Phase 2 VERITAC Trial Results

November 22, 2022



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Agenda



Topic	Participant	
Introduction	John G. Houston, Ph.D.	<i>President and Chief Executive Officer, Arvinas</i>
ARV-471: VERITAC Clinical Data Update	Ron Peck, M.D.	<i>Chief Medical Officer, Arvinas</i>
Conclusions	John G. Houston, Ph.D.	<i>President and Chief Executive Officer, Arvinas</i>
 Q&A	Includes: Chris Boshoff, M.D., Ph.D.	<i>Chief Development Officer, Oncology and Rare Disease, Pfizer Global Product Development</i>

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% (71 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)

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**

 **Add-on
therapies**

Potential future state: ARV-471

Designed to be an oral, high-potency ER degrader with favorable safety profile

CDK4/6 and other
targeted inhibitors

mTOR inhibitors
or PIK3 inhibitors

**Opportunity
for ARV-471**

Expansion

Near-term

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-3¹	Phase 3 study of palbociclib plus fulvestrant vs placebo plus fulvestrant (N=521)	0	0	34% [‡]	Expected Efficacy
acelERA²	Phase 2 study of giredestrant vs SOC[†] (N=303)	42%*	19%*	32%	
SERENA-2³	Phase 2 study of camizestrant vs fulvestrant (N=240)	50%	0	19%	
AMEERA-3²	Phase 2 study of amcenestrant vs SOC[†] (N=290)	79%* [‡]	10%* [‡]	11% [‡]	
VERONICA⁴	Phase 2 study of venetoclax plus fulvestrant vs fulvestrant (N=103)	100%	0	0	
EMERALD⁵	Phase 3 study of elacestrant vs SOC[†] (N=477)	100%	30%	22%	Expected Resistance
VERITAC	Phase 2 expansion cohorts of ARV-471 (N=71)	100%	79%	45%	

¹Lancet Oncol 2016. ²ESMO 2022. ³San Antonio Breast Cancer Symposium 2022. ⁴Clin Cancer Res 2022. ⁵J 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

ARV-471: VERITAC Phase 2 Detailed Results

Ron Peck, M.D.

Chief Medical Officer, Arvinas



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

^aEnrollment in the 200-mg QD cohort began before enrollment in the 500-mg QD cohort, ^bAnalyzed 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 <i>ESR1</i> 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)

^aBaseline ECOG PS status was unknown in 1 patient. ^bBaseline *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

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 <i>ESR1</i>	(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)

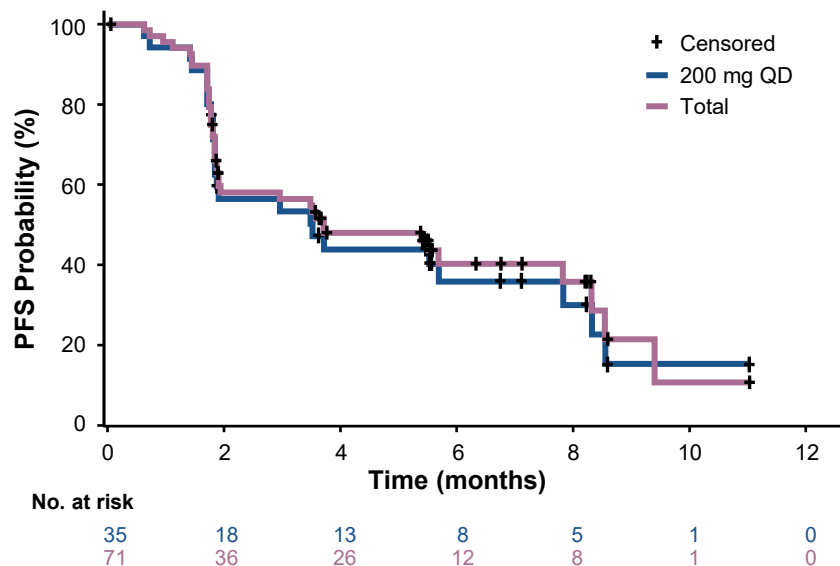
- CBR consistent with Phase 1 dose escalation data
 - Phase 1: 40% in all patients, 50% in patients with *ESR1*-mutant tumors
- Patients with WT *ESR1* (n=25) exhibited CBR rate of 20%

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

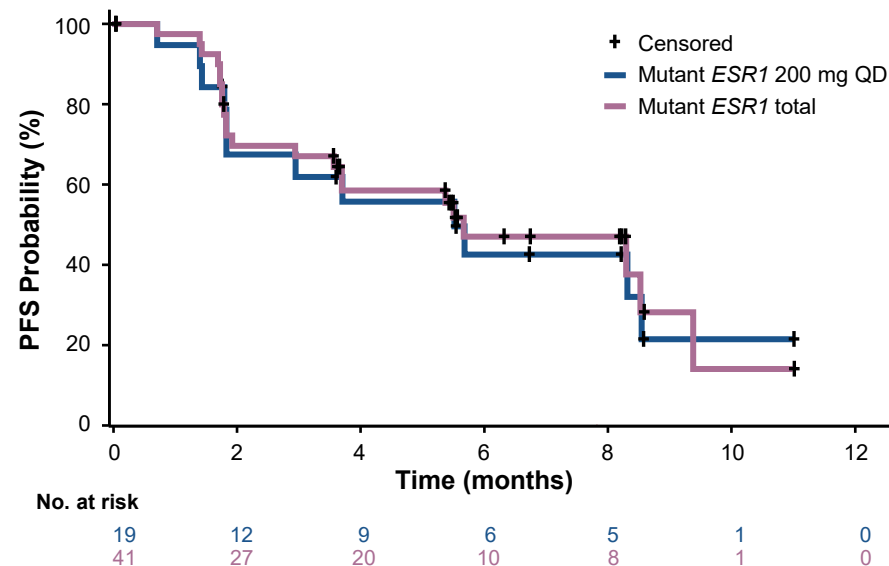


Progression-Free Survival^a (VERITAC)

	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)



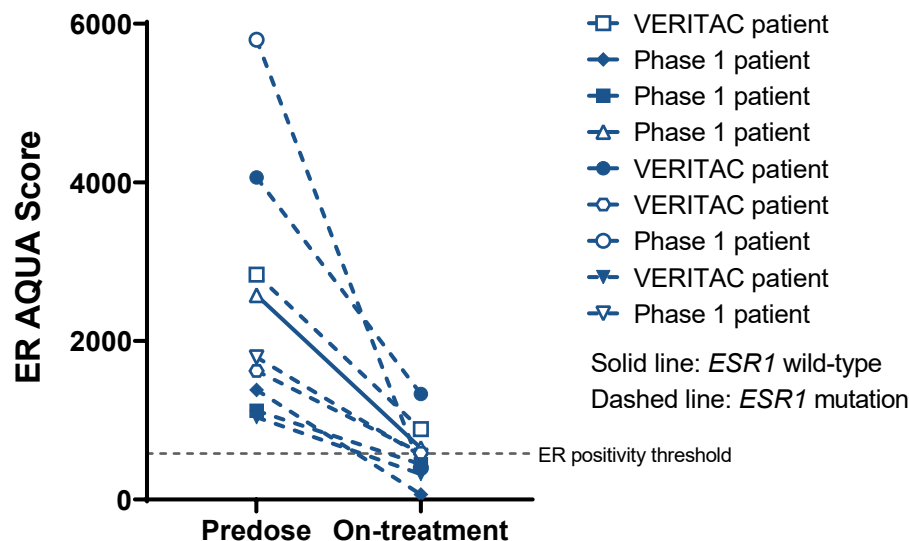
	Mutant <i>ESR1</i>	
	200 mg QD (n=19)	Total (n=41)
Events, n (%)	12 (63.2)	22 (53.7)
mPFS, mo (95% CI)	5.5 (1.8–8.5)	5.7 (3.6–9.4)



^aLimited 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%

^aER 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

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)

^aAcute respiratory failure in the setting of disease progression and unrelated to ARV-471 treatment

^bPatient had QT prolongation at baseline, received a concomitant QT-prolonging drug during ARV-471 treatment, and had hypokalemia

^cPatient 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)

TRAEs Reported in $\geq 10\%$ 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

^aGrade 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)

^bGrade 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

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

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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

^aRate 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

Conclusions

John G. Houston, Ph.D.

President and Chief Executive
Officer, Arvinas



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

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

Next milestone: Two Phase 3 registrational studies (1L and 2L)



Q&A

