205P

VERITAC update: phase 2 study of ARV-471, a PROteolysis TArgeting Chimera (PROTAC) estrogen receptor (ER) degrader in ER+/human epidermal growth factor receptor 2 (HER2)-advanced breast cancer

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Objective

- To further evaluate the clinical activity and safety of 200-mg once-daily (QD) vepdegestrant (ARV-471), an oral PROTAC ER degrader, in patients with ER+/HER2- advanced breast cancer after ≥1 prior endocrine regimen and ≥1 prior cyclin-dependent kinase (CDK)4/6 inhibitor

Key Findings

- In heavily pretreated patients (4 median prior regimens, 100% with prior CDK4/6 inhibitors, 74% with prior fulvestrant, and 74% with prior chemotherapy) with ER+/HER2- advanced breast cancer who received vepdegestrant 200 mg QD:
  - Clinical benefit rate (CBR) was 37.1% (95% CI: 21.5–55.1) in all evaluable patients (n=35) and 47.4% (95% CI: 24.4–71.1) in evaluable patients with *ESR1* mutations (n=19); for evaluable patients with wild type (WT; n=20) and mutant *PIK3CA* (n=15), CBR was 40.0% (95% CI: 19.1–63.9) and 33.3% (95% CI: 11.8–61.6), respectively
  - Median progression-free survival (PFS) was 3.5 months (95% CI: 1.8–7.8) in all patients and 5.5 months (95% CI: 1.8–8.5) in patients with *ESR1* mutations
  - Treatment-emergent adverse events (TEAEs) led to vepdegestrant discontinuation in 2 patients but no dose reductions; treatment-related AEs (TRAEs) were mostly grade 1/2
  - After 1 treatment cycle, reduction in mutant *ESR1* circulating tumor DNA (ctDNA) levels was observed in all patients, with >93% reduction in 10 of 12 (83%) evaluable patients

Conclusions

- After longer follow-up, vepdegestrant 200 mg QD continued to show clinical activity (regardless of absence or presence of mutant *PIK3CA*) and was well tolerated in heavily pretreated patients with ER+/HER2- advanced breast cancer
- The ongoing phase 3 VERITAC-2 study (NCT05654623) is evaluating vepdegestrant 200 mg QD vs fulvestrant as second-line therapy in patients with ER+/HER2- advanced breast cancer who previously received 1 line of CDK4/6 inhibitor therapy in combination with endocrine therapy
  - Please see poster 257TiP: "VERITAC-2: a global, randomized phase 3 study of vepdegestrant, a PROteolysis TArgeting Chimera (PROTAC) estrogen receptor (ER) degrader, vs fulvestrant in ER+/human epidermal growth factor receptor 2 (HER2)- advanced breast cancer" presented by Hamilton and colleagues

References

1. Flanagan JJ, et al. Presented at: SABCS; Dec 4-8, 2018; San Antonio, TX, USA. Poster P5-04-18. **2.** Hanker AB, et al. *Cancer Cell*. 2020;37(4):496-513. **3.** Nathan MR, et al. *Oncol Ther*. 2017;5(1):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. **6.** Hurvitz SA, et al. Presented at: SABCS; Dec 6-10, 2022; San Antonio, TX, USA. Oral presentation GS3-03.

Disclosure

Dr Hurvitz has served as an invited speaker for Aptitude Health, Axis Medical, Cancer Expert Now, Clinical Care Options, ICHE, MJH Associates, OBR, Peer Education, PER, PrecisCA, Primo, Projects in Knowledge, Prova Education, Research to Practice, Rockpointe, Spire Learning, Ultimate Medical Academy, Vaniam, and WebMD. She and/or her spouse have ownership interests in Ideal Implant and stocks/shares in NKMax and ROM Tech. She has received royalties from Elsevier, McGraw, Sage, Springer, Wiley, and Wolters Kluwer. Dr Hurvitz has received a research grant from Ambrx. She serves as principal investigator for Ambrx, Arvinas, AstraZeneca, Bayer, Daiichi Sankyo, Dignitana, Genentech/Roche, Gilead, GSK, Immunomedics, Lilly, Macrogenics, Novartis, OBI Pharma, Pfizer, Phoenix Molecular Designs, Ltd, Pieris, PUMA, Radius, Samumed, Sanofi, Seattle Genetics, and Zymeworks.

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Please scan this QR code with your smartphone app to view a **video of the mechanisms of action of vepdegestrant and SERDs**

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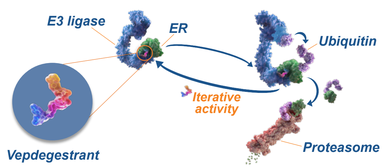
Background

- Vepdegestrant (ARV-471) is a selective, orally administered PROTAC protein degrader that binds and degrades WT and mutant ER[1]
- Vepdegestrant directly binds an E3 ubiquitin ligase and ER to trigger ubiquitination of ER and its subsequent proteasomal degradation (**Figure 1**)

Figure 1: Mechanism of action of vepdegestrant[a]



[a]General PROTAC protein degrader is shown
ER=estrogen receptor; PROTAC=PROteolysis TArgeting Chimera

- In contrast, selective ER degraders (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]
- Vepdegestrant treatment yielded substantially greater ER degradation and tumor growth inhibition than fulvestrant in breast cancer xenograft models[1]
- The phase 2 expansion (VERITAC) of a phase 1/2 study (NCT04072952) tested 2 vepdegestrant doses (200 mg QD and 500 mg QD) in heavily pretreated patients with ER+/HER2- advanced breast cancer[6]
- Vepdegestrant 200 mg QD was selected as the recommended phase 3 monotherapy dose based on comparable efficacy and favorable tolerability vs 500 mg QD and robust ER degradation (data cutoff: June 6, 2022)[6]
- Here, we present updated data for vepdegestrant 200 mg QD after 5 additional months of follow-up

Methods

- **Key eligibility criteria for VERITAC:**
  - Histologically or cytologically confirmed ER+ and HER2- advanced breast cancer
  - Measurable or nonmeasurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
  - ≥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
- **Endpoints:**
  - Primary endpoint was CBR (rate of confirmed complete response, partial response [PR], or stable disease ≥24 weeks) analyzed in patients enrolled for ≥24 weeks prior to the data cutoff
  - Secondary endpoints were objective response rate, duration of response, PFS, overall survival, safety, and pharmacokinetic parameters
  - Exploratory endpoints included *ESR1* mutation status and ctDNA
- The data cutoff date for this analysis was November 1, 2022

Results

Baseline Characteristics

- 35 patients received vepdegestrant 200 mg QD (**Table 1**)

Table 1: Patient baseline characteristics

Characteristic	Total (n=35)
Sex, n (%)	
Female	34 (97.1)
Median age, y (range)	63 (42–79)
ECOG PS, n (%)	
0	21 (60.0)
1	14 (40.0)
Visceral disease, n (%)	25 (71.4)
Sites of metastasis, n (%)	
Bone	25 (71.4)
Liver	21 (60.0)
Lung	11 (31.4)
Other	2 (5.7)
Baseline mutation status, n (%)	
ESR1	
Mutant	19 (54.3)
Wild type	16 (45.7)
PIK3CA	
Mutant	15 (42.9)
Wild type	20 (57.1)
Prior regimens, median (range)	
Any setting	4 (1–9)
Metastatic setting	3 (0–7)
Type of prior therapy, n (%)	
CDK4/6 inhibitor	35 (100)
Aromatase inhibitor	31 (88.6)
Fulvestrant	26 (74.3)
Chemotherapy	
Any setting	26 (74.3)
Metastatic setting	16 (45.7)

CDK=cyclin-dependent kinase; ECOG PS=Eastern Cooperative Oncology Group performance status; *ESR1*=estrogen receptor 1 gene; *PIK3CA*=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Efficacy

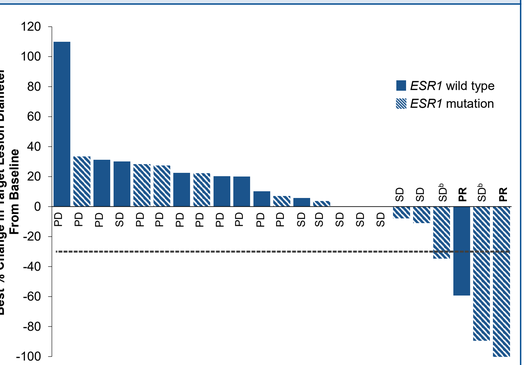
- 14 (40%) patients had received vepdegestrant for ≥24 weeks (4 [11%] for ≥48 weeks); 4 patients were ongoing at the time of data cutoff
- The CBR was 37.1% in the overall population and 47.4% in patients with mutant *ESR1* (**Table 2**)
- CBR was 40.0% (95% CI: 19.1–63.9) and 33.3% (95% CI: 11.8–61.6), respectively, in evaluable patients with WT (n=20) and mutant *PIK3CA* tumors (n=15)
- 2 patients had a confirmed PR (**Figure 2**)
- Median PFS was 3.5 months (95% CI: 1.8–7.8) in all evaluable patients and 5.5 months (95% CI: 1.8–8.5) in patients with mutant *ESR1*

Table 2: Clinical benefit rate[a]

	All patients 200 mg QD (n=35)	Mutant *ESR1* 200 mg QD (n=19)
CBR, % (95% CI)	37.1 (21.5–55.1)	47.4 (24.4–71.1)

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

Figure 2: Tumor response[a]



[a]Includes patients with measurable disease (n=23); 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; PD=progressive disease; PR=confirmed partial response; SD=stable disease

Safety

- TEAEs of any grade were reported in 91% of patients; 29% of patients experienced a grade 3/4 TEAE
  - 1 patient had a grade 5 TEAE of acute respiratory failure (unrelated to vepdegestrant treatment) in the setting of disease progression
- 2 patients discontinued vepdegestrant
  - 1 patient discontinued due to grade 3 QT prolongation; QT prolongation was present at baseline, and the patient received a concomitant QT-prolonging drug during vepdegestrant treatment and had hypokalemia
  - 1 patient discontinued due to grade 3 anemia
- No patient had dose reductions from vepdegestrant 200 mg QD due to TEAEs
- TRAEs were mostly grade 1/2 (**Table 3**)

Table 3: TRAEs reported in ≥10% of patients

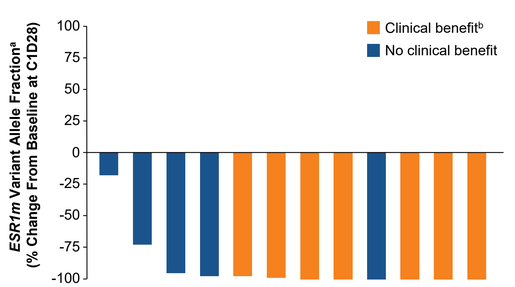
	200 mg QD (n=35)		
n (%)	Grade 1	Grade 2	Grade 3/4[a]
Any TRAE	12 (34)	15 (43)	2 (6)
Fatigue	7 (20)	7 (20)	0
Hot flush	6 (17)	0	0
Nausea	2 (6)	3 (9)	0
AST increased	3 (9)	1 (3)	0
Arthralgia	4 (11)	0	0

[a]Grade 3/4 TRAEs in the 200-mg QD cohort were grade 3 QT prolonged (n=1; same TEAE that led to discontinuation described in the bullet above) and grade 3 thrombocytopenia and grade 4 hyperbilirubinemia (n=1)
AST=aspartate aminotransferase; QD=once daily; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event

ctDNA

- After treatment with vepdegestrant 200 mg QD for 1 cycle, reduction in *ESR1* mutant allele frequency was observed in all evaluable patients, with >93% reduction in 10 of 12 (83%) patients (**Figure 3**)

Figure 3: Change from baseline in *ESR1* mutation-positive ctDNA (n=12)



[a]Summed *ESR1m* variant allele frequency
[b]Defined as confirmed complete response, partial response, or stable disease ≥24 weeks
C1D28=cycle 1, day 28; ctDNA=circulating tumor DNA; *ESR1m*=estrogen receptor 1 gene mutant