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Safety and Pharmacokinetics (PK) of Vepdegestrant in Japanese Patients With Estrogen Receptor (ER)+/Human Epidermal Growth Factor Receptor 2 (HER2)- Advanced Breast Cancer: Results From a Japanese Phase 1 Study

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Objective

- To investigate the safety, PK, and preliminary efficacy of vepdegestrant (ARV-471) in Japanese patients with estrogen receptor (ER)+/human epidermal growth factor receptor 2 (HER2)- advanced breast cancer at the recommended phase 3 dose (RP3D) of 200 mg once daily (QD)

Key Findings

- In this phase 1 study (NCT05463952), 6 female patients were treated with vepdegestrant 200 mg QD; 3 (50%) patients had received ≥3 prior regimens for advanced disease, and 5 (83%) patients received prior cyclin-dependent kinase (CDK)4/6 inhibitors for advanced disease
- No dose-limiting toxicities (DLTs) were observed
- 4 (67%) patients experienced treatment-emergent adverse events (TEAEs); all adverse events (AEs) were grade 1 or 2, and there were no dose reductions or discontinuations
  - Treatment-related AEs (TRAEs) were abdominal discomfort, anemia, dizziness, increased alanine aminotransferase, increased aspartate aminotransferase, nausea, and pruritus (1 event each); all were grade 1 except anemia (grade 2)
- Geometric mean maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve during a 24-hour dosing interval (AUC_{24}) of vepdegestrant were 630.9 ng/mL and 10,400 ng•hr/mL after a single dose and 1056 ng/mL and 18,310 ng•hr/mL after multiple doses
- 2 patients demonstrated stable disease at week 24 assessment and remained on treatment at the time of data cutoff
- 2 patients had *ESR1* mutation-positive circulating tumor DNA (ctDNA) at baseline; during treatment, variant allele fraction (VAF) was reduced for 1 patient and remained stable for the other

Conclusions

- The RP3D of vepdegestrant 200 mg QD was well tolerated in Japanese patients with ER+/HER2- advanced breast cancer, with no DLTs reported, mild TRAEs, and no discontinuations or dose reductions
- There were no obvious differences in the PK profiles between Japanese and Western patients
- Vepdegestrant is being evaluated in patients with ER+/HER2- advanced breast cancer in 2 global, randomized phase 3 studies with sites in the Asia-Pacific region:
  - The VERITAC-2 study (NCT05654623) is comparing the efficacy and safety of vepdegestrant with the selective ER degrader (SERD) fulvestrant in patients with prior CDK4/6 inhibitor therapy and endocrine therapy
  - The VERITAC-3 study (NCT05909397) is evaluating the combination of vepdegestrant plus palbociclib as first-line treatment in the advanced setting
  - See poster 73TiP (H Iwata et al) to view the study designs for VERITAC-2 and VERITAC-3

References

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Disclosure

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Background

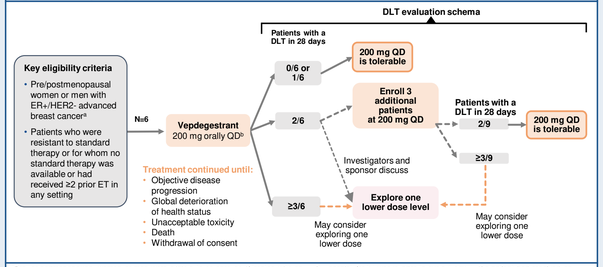
- Vepdegestrant (ARV-471) is a selective, orally administered PROteolysis TArgeting Chimera (PROTAC) ER degrader that directly binds an E3 ubiquitin ligase and ER to trigger ubiquitination of ER and its subsequent proteasomal degradation[1]
- In contrast, SERDs indirectly recruit the ubiquitin-proteasome 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]
- Vepdegestrant treatment yielded substantially greater ER degradation and tumor growth inhibition than fulvestrant in breast cancer xenograft models[1]
- In a first-in-human phase 1/2 study (NCT04072952), vepdegestrant monotherapy was well tolerated and had clinical activity in heavily pretreated patients with ER+/HER2- advanced breast cancer[6]
  - The phase 2 expansion (VERITAC) of the first-in-human study tested 2 vepdegestrant doses (200 mg QD and 500 mg QD) in heavily pretreated patients with ER+/HER2- advanced breast cancer[7]
  - Vepdegestrant 200 mg QD was selected as the phase 3 monotherapy dose based on comparable efficacy and favorable tolerability vs 500 mg QD, as well as robust ER degradation[7]
- Here, we present data from the phase 1 study of vepdegestrant 200 mg QD in Japanese patients with ER+/HER2- advanced breast cancer (NCT05463952)

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

Methods

- Patients with ER+/HER2- advanced breast cancer who were resistant to standard therapy, or for whom no standard therapy was available, or who had received ≥2 prior endocrine therapies in any setting were enrolled at 2 centers in Japan to receive vepdegestrant 200 mg QD (**Figure 1**)
- The primary objective was to evaluate the safety and tolerability of vepdegestrant at the RP3D of 200 mg QD through assessment of DLTs during the first 28-day cycle
  - Hematologic DLTs were considered grade ≥3 hematologic parameters lasting >28 days, grade ≥3 neutropenia with infection, grade 4 neutropenia lasting >5 days, febrile neutropenia, grade 3 thrombocytopenia with bleeding or requiring platelet transfusion, grade 4 thrombocytopenia, or any toxicity requiring dose interruption for ≥14 days
  - Nonhematologic DLTs included grade ≥3 toxicities, Hy's Law, grade ≥3 electrolyte abnormality lasting >72 hours or for any duration if the patient has clinical symptoms, QTcF prolongation (any grade ≥3 QT prolongation), any AE attributed to vepdegestrant requiring dose interruption for ≥14 days, or any death not clearly due to the underlying disease or extraneous causes
- Secondary objectives were to evaluate the overall safety profile, to characterize the single-dose and multiple-dose PK of vepdegestrant, and to explore preliminary antitumor activity
  - Safety evaluation included assessment of type, frequency, and severity of AEs (per Common Terminology Criteria for Adverse Events version 5.0), assessment of laboratory abnormalities, and 12-lead electrocardiograms
  - PK samples were obtained at predose and 1, 2, 4, 6, 8, 12 (optional), and 24 hours post dose on cycle 1 day 1 (after single dose) and cycle 1 day 15 (after multiple doses)
  - Tumor assessments were performed per Response Evaluation Criteria in Solid Tumors version 1.1 at baseline, every 8 weeks in the first 6 cycles, and then every 12 weeks thereafter
- An exploratory objective was to characterize baseline *ESR1* mutational status and relevant molecularly defined subsets of patients
  - Plasma samples for ctDNA analysis were collected on day 1 of cycles 1, 3, and 6 and at the end of treatment and sequenced with the FoundationOne Liquid CDx test
- The data cutoff date for this analysis was May 4, 2023

Figure 1: Study design



[a]Pre- or perimenopausal women or men were eligible to be enrolled if treated with an LHRH agonist for ≥4 weeks prior to cycle 1 day 1. If a patient had received an LHRH agonist, they were required to remain on it for the duration of the trial
[b]Vepdegestrant 200 mg was given QD with food
DLT=dose-limiting toxicity; ER=estrogen receptor; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; LHRH=luteinizing hormone-releasing hormone; QD=once daily

Results

Baseline Characteristics

- As of the data cutoff (May 4, 2023), 6 female patients had received vepdegestrant 200 mg QD and 2 patients remained on treatment; baseline characteristics are shown in **Table 1**
- Median (range) treatment duration was 9.8 weeks (6–28)
- Median (range) relative dose intensity was 100% (100%–100%) in cycle 1 and 100% (88.9%–102.4%) across all cycles

Table 1: Baseline characteristics

Characteristic	Total (N=6)
Sex, n (%)	
Female	6 (100)
Median age (range), y	58 (47–62)
Median weight (range), kg	53.2 (41.9–70.0)
ECOG PS, n (%)	
0	4 (66.7)
1	2 (33.3)
TNM at initial diagnosis, n (%)	
I	1 (16.7)
II	2 (33.3)
III	1 (16.7)
IV	1 (16.7)
Unknown	1 (16.7)
Target disease at baseline, n (%)	
Liver	4 (66.7)
Breast	1 (16.7)
Lung	1 (16.7)
Lymph node	1 (16.7)
None	1 (16.7)
Nontarget disease at baseline, n (%)	
Lymph node	4 (66.7)
Bone	3 (50.0)
Lung	3 (50.0)
Liver	2 (33.3)
Brain	1 (16.7)
Pleura	1 (16.7)
Baseline *ESR1* mutation, n (%)	
Yes	2 (33.3)
No	3 (50.0)
Unknown	1 (16.7)
Number of prior regimens, median (range)	
Any setting	4.5 (2–14)
Advanced/metastatic setting	2.5 (1–10)
Lines of prior regimens for advanced/metastatic setting, n (%)	
1	1 (16.7)
2	2 (33.3)
≥3	3 (50.0)
Type of prior therapy for advanced/metastatic setting, n (%)	
CDK4/6 inhibitor	5 (83.3)
Aromatase inhibitor	5 (83.3)
Fulvestrant	4 (66.7)
Chemotherapy	2 (33.3)

CDK=cyclin-dependent kinase; ECOG PS=Eastern Cooperative Oncology Group performance status; *ESR1*=estrogen receptor 1 gene; TNM=tumor, node, and metastasis

Safety

- No DLTs were observed at the RP3D of 200 mg QD
- 4 (66.7%) patients experienced TEAEs
  - All AEs were grade 1 or 2
- TRAEs observed in 4 patients are shown in **Table 2**; all were grade 1 except anemia (grade 2)
- No AEs led to dose reduction or discontinuation
  - 1 patient temporarily discontinued treatment for 22 days due to COVID-19

Table 2: Treatment-related adverse events (all cycles)

n (%)	Vepdegestrant 200 mg QD (N=6)			
	All Grades	Grade 1	Grade 2	Grade 3/4
Any treatment-related adverse event	4 (66.7)	3 (50.0)	1 (16.7)	0
Abdominal discomfort	1 (16.7)	1 (16.7)	0	0
Anemia	1 (16.7)	0	1 (16.7)	0
Dizziness	1 (16.7)	1 (16.7)	0	0
Increased ALT	1 (16.7)	1 (16.7)	0	0
Increased AST	1 (16.7)	1 (16.7)	0	0
Nausea	1 (16.7)	1 (16.7)	0	0
Pruritus	1 (16.7)	1 (16.7)	0	0

No patients experienced clinically significant QT prolongation
ALT=alanine aminotransferase; AST=aspartate aminotransferase; QD=once daily

Pharmacokinetics

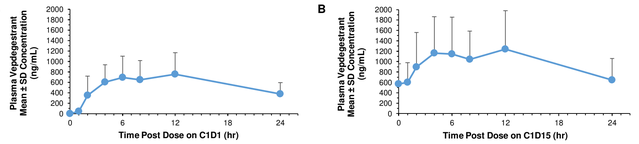
- Geometric mean C_{max} and AUC_{24} of vepdegestrant were 630.9 ng/mL and 10,400 ng•hr/mL after a single dose and 1056 ng/mL and 18,310 ng•hr/mL after multiple doses (**Table 3**)
- Mean plasma concentration profiles of vepdegestrant after a single dose and multiple doses are shown in **Figure 2**
  - One patient showed higher exposure of vepdegestrant than other patients; however, this was not associated with the frequency or severity of AEs; only grade 1 dizziness was reported as a TRAE in this patient

Table 3: Vepdegestrant PK parameters following a single dose and once-daily multiple dosing

Parameter (unit)	Vepdegestrant 200 mg QD (N=6)	
	Single dose	Multiple doses
C_{max} (ng/mL)	630.9 (57)	1056 (54)
C_{trough} (ng/mL)	NA	496.3 (57)
T_{max} (hr)	4.74 (3.75–6.28)	4.69 (3.72–6.03)
$t_{1/2eff}$ (hr)	NA	20.23 ± 6.70
AUC_{24} (ng•hr/mL)	10,400 (58)	18,310 (57)
R_{ac}	NA	1.760 (21)

Geometric mean (geometric % coefficient of variation) for all, except median (range) for T_{max} and arithmetic mean ± standard deviation for $t_{1/2eff}$.
AUC_{24}=area under the plasma concentration-time curve during a 24-hour dosing interval; C_{max}=maximum plasma concentration; C_{trough}=predose plasma concentration during multiple dosing; NA=not applicable; PK=pharmacokinetics; QD=once daily; R_{ac}=ratio of AUC_{24} after multiple doses/AUC_{24} after single dose; $t_{1/2eff}$=effective elimination half-life based on accumulation ratio; T_{max}=time to reach C_{max}

Figure 2: Vepdegestrant plasma concentration profile following (A) a single dose and (B) once-daily multiple dosing (N=6)



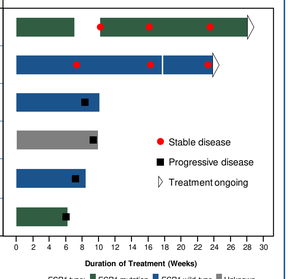
C=cycle; D=day; SD=standard deviation

Efficacy

- 2 patients demonstrated stable disease at week 24 tumor assessment (**Figure 3**), and treatment was ongoing at the time of data cutoff

Figure 3: Investigator-assessed tumor response

Patient #	Prior therapy for advanced disease			Gene mutation status at baseline		
	CDK4/6 inhibitor	Fulvestrant	Chemotherapy	*ESR1* mutation	*PIK3CA* mutation	Other mutation[a]
1	X			X (L536P)		
2	X	X				
3	X	X				*FGFR1*, *PTEN*
4				NA	NA	NA
5	X	X	X		X	*FGFR1*, *PTEN*, *TP53*
6	X	X	X	X (D538G)	X	

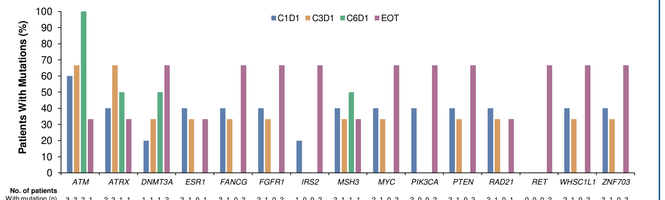


[a]Other mutation includes mutation positive of *FGFR1*, *PTEN*, or *TP53*
NA=ctDNA analysis result is not available
CDK=cyclin-dependent kinase; ctDNA=circulating tumor DNA; *ESR1*=estrogen receptor 1 gene; *FGFR1*=fibroblast growth factor receptor 1; *PIK3CA*=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*=phosphatase and tensin homolog; *TP53*=tumor protein p53

Biomarker Analyses

- The proportions of patients with mutations in key genes of interest across the study are shown in **Figure 4**
- 2 patients had *ESR1* mutation-positive ctDNA at baseline
  - For patient 1 (L536P mutation), VAF was maintained from 0.17 at baseline to 0.10 at cycle 3 day 1
  - For patient 6 (D538G mutation), VAF was reduced from 4.50 at baseline to 0.61 at the end of treatment

Figure 4: Proportion of patients with mutations in key genes[a]



[a]Genes that demonstrated mutation positive on cycle 1 day 1 and/or post dosing in ≥2 patients were selected
ATM=ATM serine/threonine kinase; *ATRX*=ATRX chromatin remodeler; C=cycle; D=day; *DNMT3A*=DNA methyltransferase 3 alpha; EOT=end of treatment; *ESR1*=estrogen receptor 1 gene; *FANCG*=FA complementation group G; *FGFR1*=fibroblast growth factor receptor 1; *IRS2*=insulin receptor substrate 2; *MSH3*=mutS homolog 3; *MYC*=MYC proto-oncogene, bHLH transcription factor; *PIK3CA*=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*=phosphatase and tensin homolog; *RAD21*=RAD21 cohesin complex component; *RET*=ret proto-oncogene; *WHSC1L1*=nuclear receptor binding SET domain protein 3; *ZNF703*=zinc finger protein 703