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First-in-human safety and activity of ARV-471, a novel PROTAC® estrogen receptor degrader, in ER+/HER2- locally advanced or metastatic breast cancer

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Objective

- To evaluate the safety and clinical activity of ARV-471, an oral estrogen receptor (ER) PROteolysis TArgeting Chimera (PROTAC®) protein degrader, in patients with ER-positive/human epidermal growth factor receptor 2-negative (ER+/HER2-) locally advanced or metastatic breast cancer who had previously received cyclin-dependent kinase (CDK)4/6 inhibitors

Key Findings

- ARV-471 was well tolerated at all dose levels, with no dose-limiting toxicities (DLTs) reported
- Most treatment-related adverse events (TRAEs) were grade 1/2
- ARV-471 showed antitumor activity in CDK4/6 inhibitor–pretreated patients with ER+/HER2- breast cancer, with a clinical benefit rate (CBR) of 40% (95% CI: 26%–56%)
- Dose-related increases in area under the curve from 0 to 24 hours (AUC_{24}) and maximum plasma concentration (C_{max}) were seen at doses up to 500 mg daily
- ARV-471 demonstrated robust ER degradation (up to 89%) at all doses up to 500 mg daily in paired biopsy samples

Conclusions

- ARV-471 has a manageable safety profile, with mostly low-grade TRAEs
- Pharmacokinetics of ARV-471 were dose-related up to 500 mg daily
- Clinical activity and pharmacodynamic data suggest ARV-471 may have superior ER degradation to fulvestrant[1–3] and has the potential to fill an unmet need for patients with ER+/HER2- breast cancer and prior treatment with CDK4/6 inhibitors
- Data support further development of ARV-471; the phase 2 VERITAC expansion cohort of ARV-471 monotherapy and a phase 1b combination cohort with palbociclib are ongoing, and phase 3 trials are planned

References

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Plain Language Summary
Please scan this Quick Response (QR) code with your smartphone app to view a plain language summary.

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Background

- There is an unmet need for better treatments for ER+ advanced breast cancer; resistance to CDK4/6 inhibitors and endocrine therapy remains a particularly acute challenge, with poor outcomes in patients who have progressed on or after these agents[3,4]
  - The CBR with fulvestrant plus venetoclax vs fulvestrant alone was only 11.8% vs 13.7% in the randomized phase 2 VERONICA study in patients with breast cancer after prior CDK4/6 inhibitor and endocrine therapy[3]
  - ≥66% of patients with metastatic breast cancer treated with CDK4/6 inhibitors develop a genomic alteration representing an ER-independent mechanism of resistance[5]
- Although fulvestrant is a standard therapy for patients with ER+ advanced breast cancer,[6] it has limitations, including its intramuscular route of administration and only 40–50% degradation of ER protein at its optimal dose[1,2]
- ARV-471, a novel, potent, selective, orally bioavailable PROTAC® protein degrader, demonstrated superior ER degradation and antitumor activity compared with fulvestrant in endocrine-sensitive and endocrine-resistant xenograft models[7]

Methods

- This is a phase 1/2, multicenter, first-in-human, open-label study (NCT04072952) of ARV-471 in patients with ER+/HER2- breast cancer
- In the phase 1 dose escalation portion (3+3 design with backfill), patients had received ≥1 prior CDK4/6 inhibitor, ≥2 prior endocrine therapies, and ≤3 prior lines of chemotherapy; ARV-471 was administered orally with food at a starting dose of 30 mg daily
  - Intrapatient dose escalations were permitted
- The primary objective of the phase 1 dose escalation study was to evaluate the safety and tolerability of ARV-471 in order to estimate the maximum tolerated dose (MTD) and select the recommended phase 2 doses
- Other objectives were to assess pharmacokinetics and pharmacodynamics and explore ARV-471's antitumor activity
- CBR (rate of confirmed complete response [CR] or partial response [PR] or stable disease [SD] ≥24 weeks) was analyzed in patients enrolled ≥24 weeks prior to the data cutoff

Results

Baseline Characteristics

- As of September 30, 2021, 60 patients were treated in the phase 1 dose escalation portion of the study with total daily ARV-471 doses ranging from 30 mg to 700 mg
- All patients received prior CDK4/6 inhibitors, 80% received prior fulvestrant, and 78% received prior chemotherapy (**Table 1**)

Table 1: Baseline characteristics

Parameter	Total (N=60)
Median age (range), years	65.5 (38–80)
ECOG performance status, n (%)*	
0	29 (48)
1	30 (50)
Sites of metastasis, n (%)	
Bone	33 (55)
Liver	23 (38)
Lung	13 (22)
Other	13 (22)
Median no. lines of prior therapy in any setting (range)†	4 (1–10)
Type of prior therapy in any setting, n (%)	
CDK4/6 inhibitor	60 (100)
Aromatase inhibitors	52 (87)
SERD	50 (83)
Fulvestrant	48 (80)
Investigational	6 (10)
Chemotherapy	47 (78)

*Baseline value missing for 1 patient.
†Median of 3 prior lines in the metastatic setting.
CDK=cyclin-dependent kinase; ECOG=Eastern Cooperative Oncology Group; SERD=selective estrogen receptor degrader.

Safety

- No DLTs or grade ≥4 TRAEs were observed; the MTD was not reached
- Of 60 patients, 37% had grade 1 TRAEs and 57% had grade ≤2 TRAEs (**Table 2**)
- There were six grade 3 TRAEs in four patients (headache lasting 1 day, single occurrence of asymptomatic increased amylase and lipase, nausea and asymptomatic QTc prolongation, and venous embolism after a minor procedure)
  - The patient with grade 3 venous embolism was the only patient who discontinued ARV-471 due to a TRAE, and the patient with grade 3 nausea was the only patient with a dose reduction due to a TRAE (500 mg to 400 mg)

Table 2: Treatment-related adverse events reported in ≥10% of patients overall

	30 mg (n=3)		60 mg (n=3)		120 mg (n=7)		180/200 mg (n=11)		360 mg (n=15)		500 mg (n=17)		700 mg (n=4)		Total (N=60)	
TRAE, n (%)	Gr 1/2	Gr 3	Gr 1/2	Gr 3	Gr 1/2	Gr 3	Gr 1/2	Gr 3	Gr 1/2	Gr 3	Gr 1/2	Gr 3	Gr 1/2	Gr 3	Gr 1/2	Gr 3
Any TRAE	0	0	3 (50)	0	6 (86)	0	6 (55)	1 (9)	10 (67)	1 (7)	7 (41)	2 (12)	2 (50)	0	34 (57)	4 (7)
Nausea	0	0	2 (33)	0	2 (29)	0	4 (36)	0	3 (20)	0	4 (24)	1 (6)	1 (25)	0	16 (27)	1 (2)
Fatigue	0	0	1 (17)	0	0	0	1 (9)	0	3 (20)	0	5 (29)	0	2 (50)	0	12 (20)	0
Vomiting	0	0	0	0	2 (29)	0	1 (9)	0	2 (13)	0	1 (6)	0	0	0	6 (10)	0
AST increased	0	0	0	0	1 (14)	0	2 (18)	0	0	0	1 (6)	0	2 (50)	0	6 (10)	0

AST=aspartate aminotransferase; Gr=grade; TRAE=treatment-related adverse event.

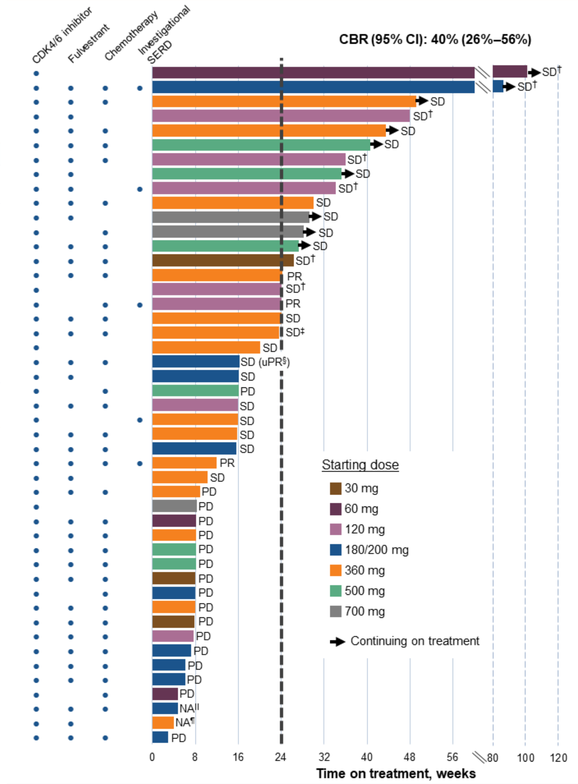
Efficacy

- The CBR (rate of confirmed CR or PR or SD ≥24 weeks) was 40% (95% CI: 26%–56%) in 47 evaluable patients; 3 patients had confirmed PRs (**Figures 1–3**)
- 14 patients were ongoing at the time of data cutoff, including 2 who have been on treatment for >18 months

Pharmacokinetics

- Preliminary pharmacokinetic data showed dose-related increases for AUC_{24} and C_{max} from 30 mg to 500 mg daily doses (**Table 3**); mean exposure on Day 15 exceeded the nonclinical efficacious range at doses ≥60 mg daily

Figure 1: Clinical benefit rate in evaluable patients (n=47)*



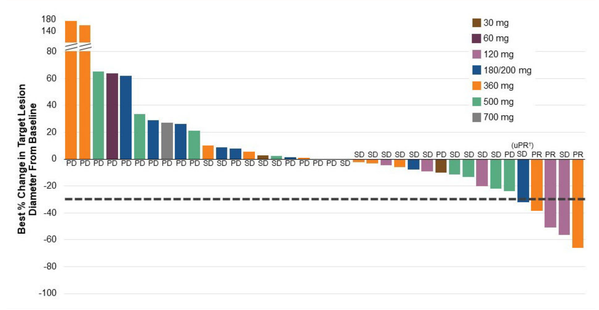
*CBR is the rate of confirmed CR or PR or SD ≥24 weeks; excludes patients unable to complete cycle 1 due to reasons other than PD, toxicity, or death.
†Patient had dose escalation from starting dose.
‡Week 24 imaging assessment performed at 23.4 weeks (within the window allowed per protocol).
§Patient had disease progression on subsequent scan and discontinued treatment.
‖Patient discontinued treatment due to clinical progression before first on-study scan.
¶Patient discontinued treatment due to venous embolism before first on-study scan.
CBR=clinical benefit rate; CDK=cyclin-dependent kinase; NA=not available; PD=progressive disease; PR=confirmed partial response; SD=stable disease; SERD=selective estrogen receptor degrader; uPR=unconfirmed partial response.

Table 3: Preliminary ARV-471 pharmacokinetic parameters* on Day 15

Parameter, mean, (% CV)	30 mg QD (n=3)	60 mg QD (n=3)	120 mg QD (n=7)	180 mg QD (n=6)	200 mg QD (n=4)	360 mg QD (n=15)	500 mg QD (n=3)	250 mg BID (n=7)	700 mg† (n=3)
AUC_{24}, ng·h/mL‡	4138 (23)	7391 (15)	13,854 (13)	20,043 (30)	14,762 (37)	26,794 (26)	33,896 (54)	22,711 (25)	21,220 (58)
C_{max}, ng/ml	224 (24)	405 (8)	800 (6)	1094 (26)	874 (49)	1548 (24)	2563 (76)	2253 (25)	2133 (50)

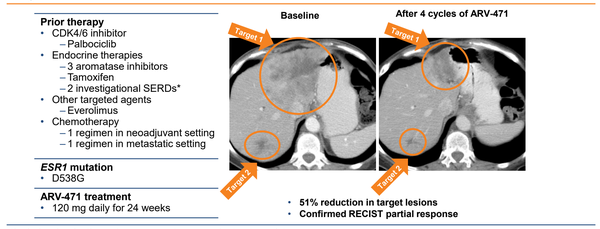
*Performed using noncompartmental analysis methods; as of September 29, 2021.
†400 mg AM/300 mg PM.
‡AUC_{12} for 250 mg BID and 700 mg dosing cohorts.
AUC_{12}=area under the curve from 0 to 12 hours; AUC_{24}=area under the curve from 0 to 24 hours; BID=twice daily; C_{max}=maximum plasma concentration; CV=coefficient of variation; QD=once daily.

Figure 2: Antitumor activity (best percentage change from baseline in sum of target lesions) in response-evaluable patients (n=38)*



*Patients with measurable disease at baseline who had a baseline and ≥1 on-treatment scan.
†Patient had disease progression on subsequent scan and discontinued treatment.
PD=progressive disease; PR=confirmed partial response; SD=stable disease; uPR=unconfirmed partial response.

Figure 3: Patient with confirmed partial response

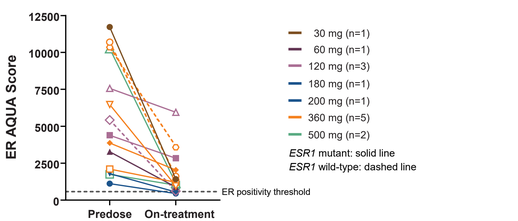


*Includes 1 selective estrogen receptor-α covalent antagonist.
CDK=cyclin-dependent kinase; RECIST=Response Evaluation Criteria in Solid Tumors; SERD=selective estrogen receptor degrader.

Biomarkers

- Robust ER degradation (up to 89%) was observed at all doses up to 500 mg daily, regardless of *ESR1* mutation status (**Figure 4**)
- Median and mean ER degradation across dose levels was 67% and 64%, respectively

Figure 4: ER degradation* (n=14)



*Data available as of September 3, 2021; median time on treatment at biopsy: 31 days (range: 16–77). 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.
AQUA=automated quantitative analysis; ER=estrogen receptor; QIF=quantitative immunofluorescence.