

# 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<sub>24</sub>) and maximum plasma concentration (C<sub>max</sub>) 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<sup>1–3</sup> 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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## 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<sup>3,4</sup>
  - 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<sup>3</sup>
  - ≥66% of patients with metastatic breast cancer treated with CDK4/6 inhibitors develop a genomic alteration representing an ER-independent mechanism of resistance<sup>5</sup>
- Although fulvestrant is a standard therapy for patients with ER+ advanced breast cancer,<sup>6</sup> it has limitations, including its intramuscular route of administration and only 40–50% degradation of ER protein at its optimal dose<sup>1,2</sup>
- 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<sup>7</sup>

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

<sup>\*</sup>Baseline value missing for 1 patient.  
<sup>†</sup>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

TRAE, n (%)	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)	
	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.

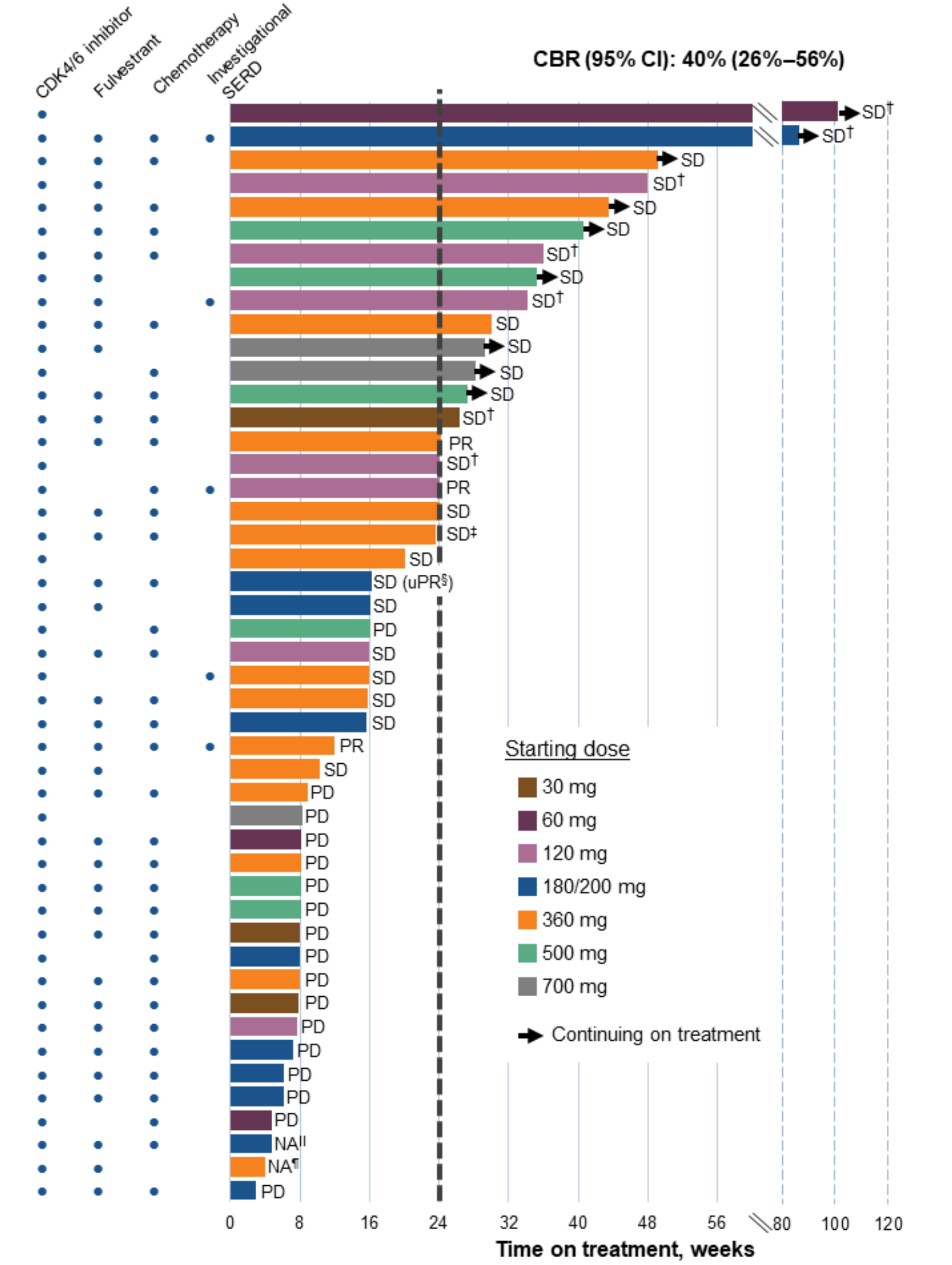
### Efficacy

- 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<sub>24</sub> and C<sub>max</sub> 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)\*



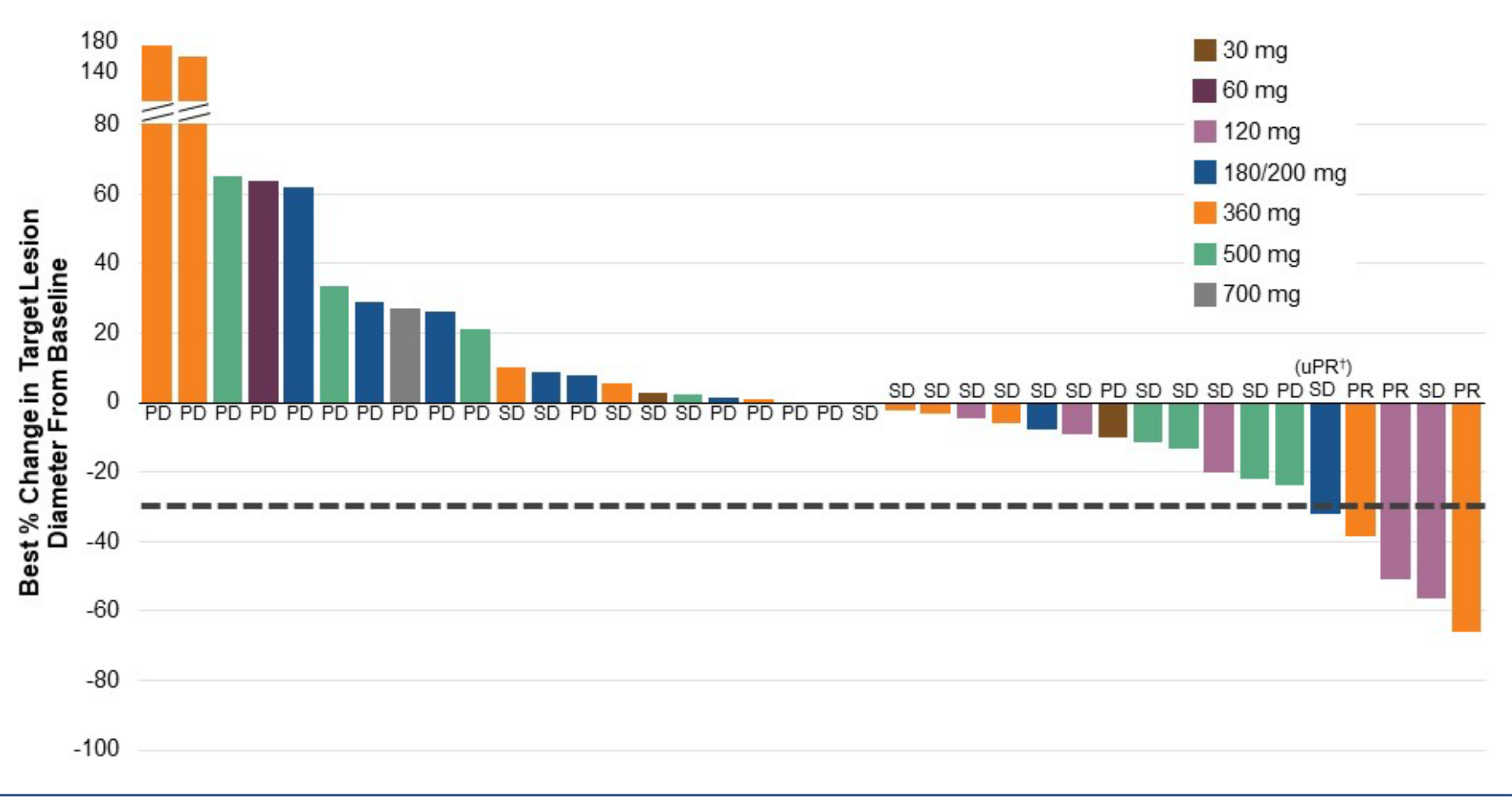
\*CBR is the rate of confirmed CR or PR or SD ≥24 weeks; excludes patients unable to complete cycle 1 due to reasons other than PD, toxicity, or death.  
<sup>†</sup>Patient had dose escalation from starting dose.  
<sup>‡</sup>Week 24 imaging assessment performed at 23.4 weeks (within the window allowed per protocol).  
<sup>§</sup>Patient had disease progression on subsequent scan and discontinued treatment.  
<sup>||</sup>Patient discontinued treatment due to clinical progression before first on-study scan.  
<sup>¶</sup>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 <sup>†</sup> (n=3)
AUC <sub>24</sub> , ng·h/mL <sup>‡</sup>	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 <sub>max</sub> , ng/ml	224 (24)	405 (8)	800 (6)	1094 (26)	874 (49)	1548 (24)	2563 (76)	2253 (25)	2133 (50)

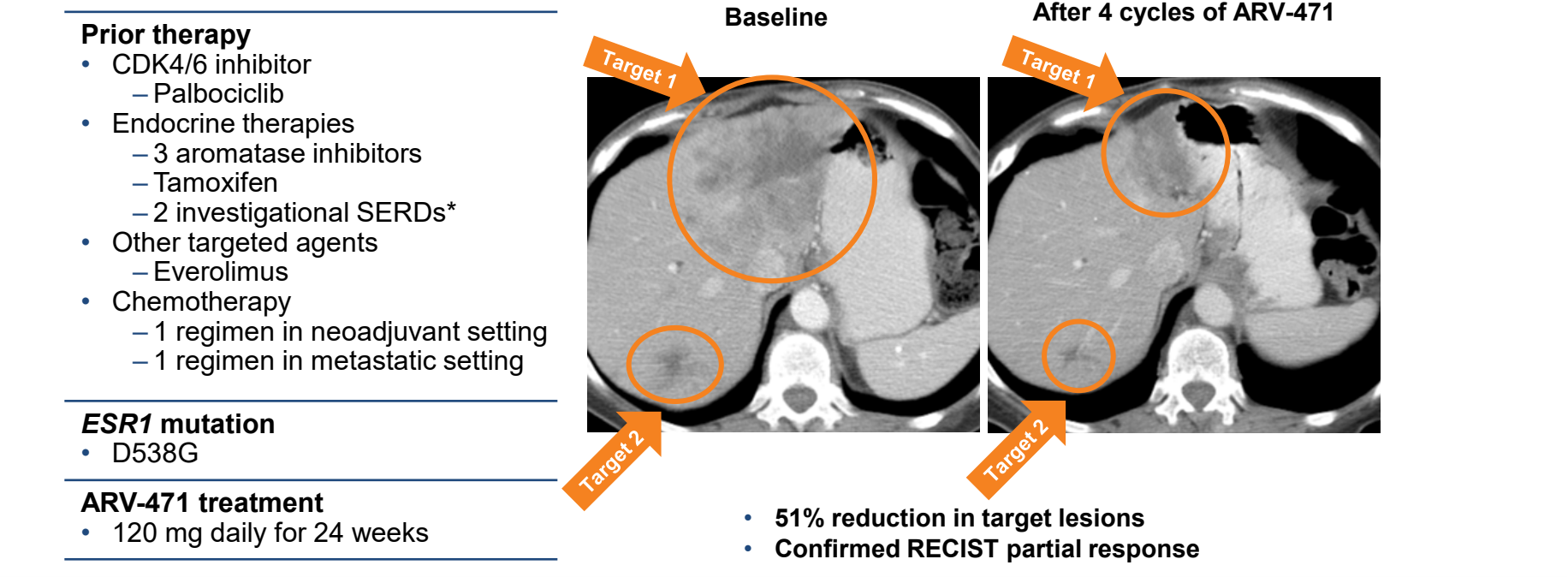
\*Performed using noncompartmental analysis methods; as of September 29, 2021.  
<sup>†</sup>1400 mg AM/300 mg PM.  
<sup>‡</sup>AUC<sub>12</sub> for 250 mg BID and 700 mg dosing cohorts.  
AUC<sub>12</sub>=area under the curve from 0 to 12 hours; AUC<sub>24</sub>=area under the curve from 0 to 24 hours; BID=twice daily; C<sub>max</sub>=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.  
<sup>†</sup>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

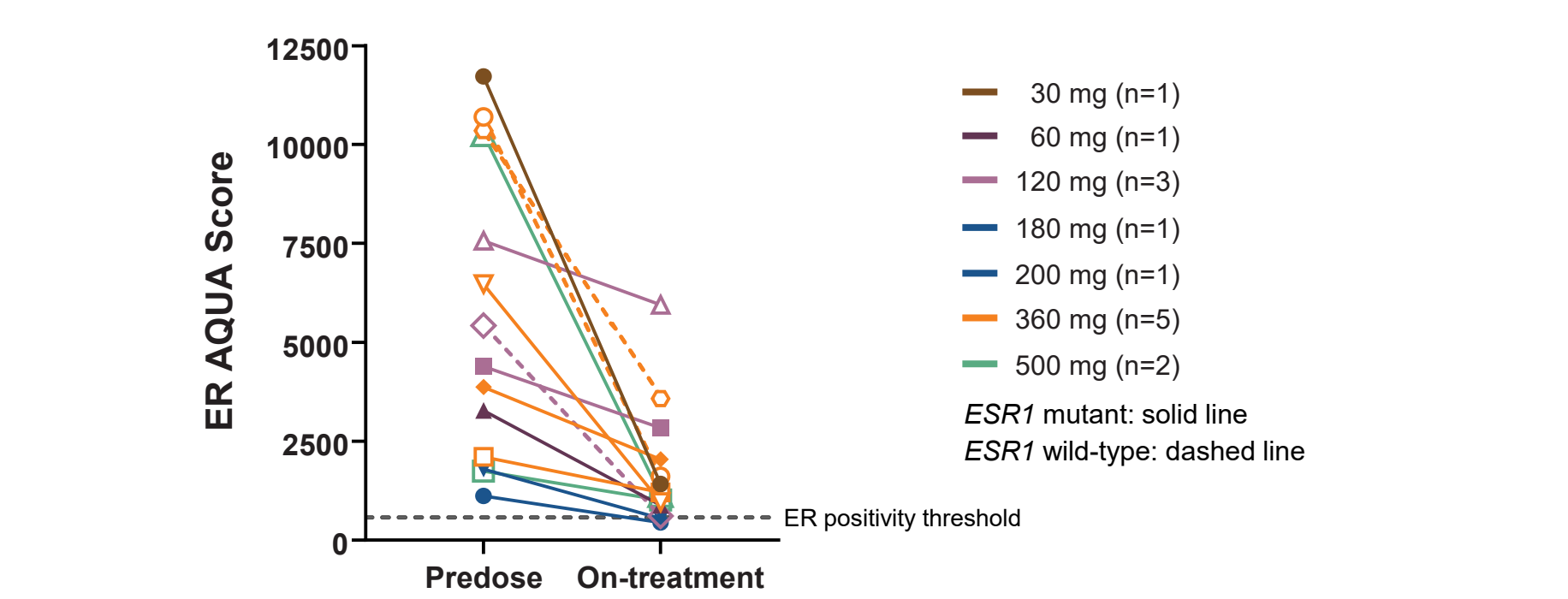


\*Includes 1 selective estrogen receptor-α covalent antagonist.  
CDK=cyclin-dependent kinase; RECIST=Response Evaluation Criteria in Solid Tumors; SERD=selective estrogen receptor degrader.

### 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.